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In The

Supreme Court of the United States

October Term, 1996

TANABE SEIYAKU CO., LTD.
AND MARION MERRELL DOW, INC.,

Petitioners,

v.

UNITED STATES INTERNATIONAL
TRADE COMMISSION,

Respondent,

-and-

ORION CORPORATION FERMION, COPLEY
PHARMACEUTICALS, INC., INTERCHEM
CORPORATION AND RHONE-POULENC RORER, INC.,

Respondents.

**On Petition For A Writ Of Certiorari
To The United States Court Of Appeals
For The Federal Circuit**

APPENDIX TO PETITION FOR A WRIT OF CERTIORARI VOLUME II, PAGES 251-462

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III. INFRINGEMENT

A. The Profarmaco Process Does Not Infringe Claim 1 of the '035 Patent

1. The Development of the Profarmaco Process

FF CP 1. In approximately late 1982, Profarmaco began work to synthesize diltiazem. Piselli, Tr. 1966.

FF CP 2. Using the German counterpart to the '257 patent, one of the Profarmaco scientists, Dr. Piselli, ran several experiments involving the N-alkylation step. Piselli, Tr. 1967-1969, 1998.

FF CP 3. In these, he used sodium hydride and anhydrous ("DMF") to become more familiar with the N-alkylation of TZP. Piselli, Tr. 1967-1969, 1998-99.

FF CP 4. Knowing that sodium hydride is unacceptable for commercial scale synthesis, Dr. Piselli almost immediately tried potassium carbonate and DMF. Piselli, Tr. 1967-69.

FF CP 5. The potassium carbonate/DMF combination – which was the first one that Dr. Piselli tried – was selected based on a 1978 article by Professor Makosza, an organic chemist known as the "inventor of phase transfer," which specifically disclosed the use of potassium carbonate and DMF in similar reactions. Piselli, Tr. 1967-69; RX 3025.

FF CP 6. The Makosza article described the possibility of replacing the reagents described in the '257 patent with potassium carbonate and DMF. Piselli, Tr. 1967; RX 3025.

FF CP 7. The article specifically described the advantages of potassium carbonate/DMF over sodium hydride, including the eliminations of potentially dangerous reactions caused by anhydrous organic solvents. Piselli, Tr. 1968; RX 3025.

FF CP 8. Dr. Piselli had previously used such a system at Profarmaco and he therefore followed Makosza's suggestions and tried potassium carbonate/DMF in his first experiments. Piselli, Tr. 1969.

FF CP 9. This potassium carbonate/DMF process – the first one that Dr. Piselli tried – was successful. Piselli, Tr. 1969.

FF CP 10. Within two months, Dr. Piselli had developed an industrial process using potassium carbonate/DMF. Piselli, Tr. 1969.

FF CP 11. Profarmaco used this process for producing bulk diltiazem from approximately mid-1983 to July 15, 1986. Piselli, Tr. 1970; RPX 4026.

FF CP 12. In order to increase the consistency of the yield, Profarmaco experimented with the addition of water to the reaction and found that [C] % by volume of water caused more consistent yields. During the summer of 1986, Profarmaco therefore modified its process to include the addition of [C] % water to its potassium carbonate/DMF process. Piselli, Tr. 1969-1970, 2001-2002; RPX 4026.

FF CP 13. Shortly after December 30, 1986, Profarmaco first learned from a French pharmaceutical firm,

Sanofi, of the Tanabe European Patent Application corresponding to the '035 patent. Russolo, Tr. 1924; Piselli, Tr. 2001; RX 3930C.

FF CP 14. This was the first time anyone at Profarmaco became aware of the existence of the '035 patent or any of its counterparts. Russolo, Tr. 1924; Piselli, Tr. 1970, 2001.

FF CP 15. Profarmaco reviewed this patent application and after such review concluded that its potassium carbonate/DMF process did not infringe. Russolo, Tr. 1934.

FF CP 16. Profarmaco therefore continued using this process for five additional years. Russolo, Tr. 1934.

FF CP 17. In April 1989, after expiration of the '257 patent and with the end of MMD's Waxman-Hatch exclusivity on the horizon, Gyma, Profarmaco's exclusive agent in the United States, wrote to MMD requesting disclosure of any process patents which MMD contended might cover processes for the manufacture of diltiazem. RX 3947C at 214-215; Russolo, Tr. 1924-25.

FF CP 18. MMD responded shortly thereafter by identifying four patents, including the '035 patent. RX 3947C at 216; Russolo, Tr. 1924-25.

FF CP 19. Gyma forwarded MMD's process patent disclosure letter to Profarmaco for review. Russolo, Tr. 1924-25.

FF CP 20. Profarmaco, after reviewing the '035 patent, continued to use its potassium carbonate/DMF process. Russolo, Tr. 1934.

Receipt by Profarmaco of the EPO Comparative Test Report

FF CP 21. On June 13, 1991, Profarmaco received from its Italian patent attorneys (in connection with an inquiry from Profarmaco on a different matter) Tanabe's October 1, 1984 submission to the European Patent Office, including the Comparative Test Report. Russolo, Tr. 1925-27; RX 4032-C.

FF CP 22. Dr. Russolo, Profarmaco's Managing Director and General Manager, testified that, Profarmaco is a conservative company, and immediately decided to ascertain whether it could develop a process using a base not specified in the '035 patent claims and, particularly, bases and solvents that Tanabe had expressly represented to the EPO not to be the subject of its invention. Russolo, Tr. 1916-1917, 1925-1927.

FF CP 23. On June 27, 1991, two weeks after receipt of the Comparative Test Report, Profarmaco held an R&D meeting attended by, among others, Drs. Russolo and Piselli. Russolo, Tr. 1927-29; Piselli, Tr. 1970-71; RX 3928-C.

FF CP 24. At that meeting, Dr. Piselli was directed to try to develop an N-alkylation process using sodium carbonate as the base. Russolo, Tr. 1927-29; Piselli, Tr. 1970-71.

FF CP 25. Specifically, the meeting minutes state: "try the attachment of the chlorobase [*i.e.*, 2-dimethylaminoethyl-chloride ("DMC")] with sodium carbonate/DMF with different percentages of water." RX 3928-C; Russolo, Tr. 1928-29; Piselli, Tr. 1970-71.

FF CP 26. Sodium carbonate was chosen as a target base because Tanabe had identified the base in the Comparative Test Report as being outside the scope of its invention. Russolo, Tr. 1928-29.

FF CP 27. Profarmaco therefore viewed the use of sodium carbonate as a "zero-risk situation by using what inventors were saying not to be part of the invention." Russolo, Tr. 1926-1927.

FF CP 28. DMF was identified because that was the solvent that Profarmaco was then using in its current potassium carbonate/DMF process which was "a very good process." Russolo, Tr. 1928-29; Piselli, Tr. 1973.

FF CP 29. Four days after this R&D meeting, on July 1, 1991, Dr. Piselli conducted the first experiment using sodium carbonate in the period following receipt of the Comparative Test Report. Piselli, Tr. 1972; RX 3926C; RX 3932C.

FF CP 30. Dr. Piselli used sodium carbonate and DMF with C percent water. RX 3926 at Prof 436; Russolo, Tr. 1929-30; Piselli, Tr. 1972.

FF CP 31. During approximately the next eight months, Profarmaco was able to develop a new process for N-alkylating TZP using sodium carbonate as the base. Piselli, Tr. 1971-1972; RX 3926C; RX 3932C.

FF CP 32. In developing this process, Profarmaco conducted approximately 100 experiments. Piselli, Tr. 1972; RX 3932C.

FF CP 33. Profarmaco experimented by including and not including a phase transfer catalyst, by conducting the reaction at various temperatures, by varying

times, by using various solvents, and by adding or removing water. Piselli, Tr. 1973-74; RX 3932-C.

FF CP 34. Experimental evidence provided by complainants in this investigation shows that water removal is not critical in order to get a low yield from the Profarmaco process. Taber Tr. 2094-95.

FF CP 35. Profarmaco discovered during the course of these experiments that only by removing water (through azeotropic distillation) could Profarmaco achieve an industrially valid high-yield process. Piselli, Tr. 1975.

FF CP 36. Dr. Piselli characterized the removal of water as very important and essential. Piselli, Tr. 1975.

FF CP 37. If water is not removed from the current Profarmaco process, the reaction is "never complete" and there are by-products and impurities. Piselli, Tr. at 1975.

FF CP 38. Profarmaco also discovered that if the temperature of the reaction is less than [C] °[C], then the N-alkylation reaction cannot be completed. Piselli, Tr. at 1976.

FF CP 39. During the next eight months, Profarmaco scientists conducted approximately 100 experiments with different base/solvent combinations, and by February 1992, determined to use sodium carbonate and toluene, a base and a solvent, both of which were expressly identified by Tanabe in the Comparative Test Report as not included within its invention. Russolo, Tr. 1930; RX 3928C at 312, 315.

FF CP 40. On March 6, 1992, the sodium carbonate and toluene process went to the Pilot Plant. RX 3016C at Prof 166.

FF CP 41. By June 4, 1992, that process had been prepared for production and was ready for use. Piselli, Tr. 1978; RX 3928C at 316.

The Profarmaco Sodium Carbonate/Toluene Process

FF CP 42. Profarmaco conducts its process for manufacturing bulk diltiazem in a [C] reactor vessel with a volume of [C] cubic meters. Piselli, Tr. 1979-80.

FF CP 43. The reactor vessel contains a distillation column, [C], and a variety of other equipment. The distillation device which allows for azeotropically distilled vapors to be cooled, condensed, and then either removed from the system, or returned to the reactor vessel is known as a Markusson trap. Piselli, Tr. 1978-1980; RX 3996.

FF CP 44. In the step immediately preceding N-alkylation, Profarmaco carries out the [C]. Profarmaco first charges [C]. Profarmaco then [C]. Following this step, Profarmaco allows the contents of the reactor vessel [C], which results in the formation of two phases: a lower aqueous phase and an upper phase containing [C]. The Profarmaco operator, following the separation, [C]. Following this procedure, the operator causes [C], thus removing any last traces or droplets of water which may have adhered to the sides of the reactor vessel. Any water that is gathered as a result of [C] is then discharged by the operator [C]. Piselli, Tr. 1979-1980; RX 3996(a).

FF CP 45. The next step is the N-alkylation. That process is carried out in the same reactor vessel. The reactor vessel already contains DMC free base in a toluene solution. To that solution Profarmaco adds sodium carbonate which, by its specification, may not contain more than [C]% water by weight. It also adds TZP, which is prepared at Profarmaco, and which is heated by Profarmaco to remove all water. Piselli, Tr. 1980-82, 1986; RX 3996(b).

FF CP 46. Once the TZP and sodium carbonate have been added to the toluene solution containing DMC base, the operator heats the reactor vessel as quickly as possible using the maximum amount of steam flowing through the jackets surrounding the reactor vessel. At [C]°, the operator reduces the steam flow so that the inside temperature will reach about [C]°[C] without the reactor's contents overflowing. Through thermal inertia, the reaction mixture increases in temperature to approximately [C]° and the reaction mixture is then heated to [C]°. It takes [C] for the reaction mixture to reach [C]°;

[C] for the reaction mixture to reach [C]°; and the reaction mixture is then heated at a [C]° for [C] hours. Piselli, Tr. 1982-83; RX 3996(b).

FF CP 47. At the [C]° range, the water/toluene solution begins to distill azeotropically. Profarmaco begins to see carbon dioxide evolution at approximately [C]° and begins to see water collecting in the Markusson trap also at approximately [C]°. Because water is heavier than toluene, the water collects in the Markusson trap while the toluene returns to the reaction vessel. Piselli, Tr. 1983-84.

FF CP 48. Profarmaco observed in the R&D laboratory a relationship between carbon dioxide evolution and N-alkylation. Profarmaco has observed that the N-alkylation reaction takes place while carbon dioxide evolution is occurring. Piselli, Tr. 1984-85.

FF CP 49. Profarmaco takes five separate steps to prevent water from entering the reactor vessel and to remove water created during N-alkylation step. RX 4024-C; RX 3996(a); RX 3996(b); Piselli, Tr. 1985-87, 1977-81. Specifically:

1. during the [C] step, which immediately precedes N-alkylation, the Profarmaco operator [C] and to settle into two phases, the lower of which is water. That aqueous phase is then discharged [C]. RPX 4024-C; RX 3996(a); Piselli, Tr. 1980.

2. The operator then causes [C]." These last traces of water are then discharged [C] to make sure that there is no water in the reactor. RPX 4024(c); RX 3996(a); Piselli, Tr. 1980.

3. During the N-alkylation step, Profarmaco adds to the reactor vessel (which already contains a toluene solution containing [C]) TZP which Profarmaco has dried by heating. Piselli, Tr. 1981-82; RX 4024-C; RX 3996(a).

4. [C]. Piselli, Tr. 1981-82; RPX 4024-C; RPX 3996(a).

5. [C] Piselli, Tr. 1985-86, 1978-79; RX P4024-C.

2. Differences Between the Profarmaco Process and the '035 Process

FF CP 50. The differences between the Profarmaco process currently employed to manufacture bulk diltiazem in the N-alkylation step and the processes claimed in the '035 patent (and in the Examples contained in the patent) include the following:

a) Profarmaco uses sodium carbonate as a base; the '035 patent specifies potassium carbonate and potassium hydroxide;

b) Profarmaco uses toluene as a solvent; the '035 patent uses acetone and lower alkyl acetates, or mixtures of those solvents and water;

c) according to complainants' *theory* of the case, the '035 patent process operates in the presence of water, and calls for the optional addition of water; Profarmaco's process requires that water be removed constantly throughout the N-alkylation reaction and no water is specifically added.

d) Profarmaco's process is conducted at a temperature of approximately [C]°; the '035 processes are conducted at a maximum of 77°. CX 1 ("035 patent, col. 2, line 62).

e) in the Profarmaco process, Profarmaco arrives at a solution in toluene of the intermediate; Profarmaco is therefore ready to conduct the subsequent acetylation reaction in the same reactor vessel using the same reactants. By contrast, in the '035 process the intermediate is isolated.

See Piselli, Tr. 1986-87.

a. Solvents

FF CP 51. In comparing the solvent system of toluene to either acetone or ethyl acetate, "there are certainly differences that one can point to in the properties of these solvents." Gokel, Tr. 698.

FF CP 52. According to complainant's expert Dr. Gokel, "the key difference" of the Profarmaco process from the '035 process is the use of toluene as the solvent. Gokel, Tr. 764.

FF CP 53. The information reported in Dr. Gokel's report entitled "Fermion and Profarmaco Versions of Tanabe Diltiazem Synthesis" reflects what Dr. Gokel "constructed to aid [his] thinking at an early stage" in the present litigation. In determining the equivalence between the Fermion and Profarmaco processes with the '035 process, Dr. Gokel considered many parameters relating to the solvents used for the N-alkylation reaction. One of the parameters that Dr. Gokel considered and thought might influence his opinion was solvent polarity parameters, while another was a comparison of the water miscibilities of the different solvents. Dr. Gokel also listed and considered dipole moments and dielectric constants for the different solvents. Dr. Gokel summarized all of the different values in a solvent table on pages 13-15 of his report. CX 606; Gokel, Tr. 810-15.

FF CP 54. When looking at the solvent tables included in Dr. Gokel's report entitled "Fermion and Profarmaco Versions of Tanabe Diltiazem Synthesis," Dr. Gokel compared the relevant values of one solvent with a

second solvent, as determined by the same methodology, same tester, same equipment, etc. for the different solvents. CX 606; Gokel, Tr. 814-15.

Toluene is Substantially Different in Structure From the '035 Carbonyl Solvents

FF CP 55. The predominant structural feature of each of the solvents claimed in the '035 patent is the presence of a carbonyl group, which is shown enclosed by the dotted lines in the following formulas:

[Diagram Omitted In Printing]

RRX 3983; Taber, Tr. 2058-59.

FF CP 56. Toluene is an aromatic hydrocarbon whose structure is illustrated by the formula:

[Diagram Omitted In Printing]

RPX 3987.

FF CP 57. Toluene contains neither a carbonyl group nor any structure analogous to a carbonyl. Toluene is not a ketone (like acetone) or an ester (like an alkyl acetate). Taber, Tr. 2145; Gokel, Tr. 702.

FF CP 58. The oxygen atoms in the carbonyls of the solvents claimed in the '035 patent have two unbonded pairs of electrons which can be donated to positively charged species ("cations"), such as potassium ions (K+), as depicted below:

[Diagram Omitted In Printing]

RX 3983; Taber, Tr. 2059.

FF CP 59. The second oxygen atom in an alkyl acetate also possesses two pairs of unbonded electrons that can be donated. RX 3983; Taber, Tr. 2059.

The '035 Carbonyl Solvents Are Good Donor Solvents Whereas Toluene Is Not

FF CP 60. A donor solvent is a solvent which can donate electron density to stabilize an electron deficient species such as a cation. A donor solvent provides stabilization to an electron deficient species, such as a sodium or potassium cation, which are both electron deficient. Gokel, Tr. 702.

FF CP 61. The '035 carbonyl solvents are good donor solvents. RPX 3984; Taber, Tr. 2060; Taylor, Tr. 2606.

FF CP 62. Toluene is a very poor donor solvent. RPX 3984; Taber, Tr. 2060, 2145.

FF CP 63. A donor solvent is "a material that has a polar functional group that can solvate a Lewis acid entity." A Lewis acid entity would include a potassium ion. Gokel, Tr. 802.

FF CP 64. Acetone and lower alkyl acetates are stronger donors than toluene. Gokel. Tr. 806.

FF CP 65. Because '035 carbonyl solvents can donate electrons, particularly when they contain water, they are able to solvate (or solubilize) and thus stabilize cations of inorganic bases, such as the potassium bases of the '035 patent. Taber, Tr. 2058, 2059.

FF CP 66. Potassium bases are more soluble in carbonyl solvents than are sodium bases. RX 4038C; Taber, Tr. 2147; Kende, Tr. 1455.

FF CP 67. Because of its poor donorability, toluene cannot effectively solvate (or solubilize) and thus stabilize cations of inorganic bases, such as potassium ions or sodium ions. RX 4034; Taber, Tr. 2061-2065.

FF CP 68. Sodium carbonate is not soluble in toluene. Taber, Tr. 2093.

The '035 Carbonyl Solvents Possess Medium Polarity Whereas Toluene Is Nonpolar

FF CP 69. The '035 carbonyl solvents, methyl acetate, acetone and ethyl acetate range in donor number from 16.4 to 17.1. RPX 3984; Taber, Tr. 2060.

FF CP 70. The donor number for toluene is 0.1. RPX 3984; Taber, Tr. 2060.

FF CP 71. The '035 carbonyl solvents are more than 160 times better donors than is toluene. RPX 3984

FF CP 72. The '035 carbonyl solvents, methyl acetate, ethyl acetate and acetone, are of medium polarity, having dipole moments ranging between 5.7 and 9.0 and dielectric constants ranging from 6.0 to 20.56. RPX 3985

FF CP 73. Toluene is a non-polar solvent, having a dipole moment of 1.0 and dielectric constant of 2.38. RPX 3985; Taber, Tr. 2145; Gokel, Tr. 810.

FF CP 74. Because water is soluble in the '035 carbonyl solvents, it increases the dielectric constant of the '035 carbonyl solvents. Taber, Tr. 2067.

FF CP 75. Ionic species are solvated and stabilized better by polar solvents than by non-polar solvents. Gokel, Tr. 810.

FF CP 76. Toluene, being a non-polar solvent, lacks the ability to dissolve inorganic bases. Taber, Tr. 2064-65.

The '035 Solvents and Water Are Substantially Soluble Within Each Other Whereas Toluene and Water Are Not

FF CP 77. The '035 carbonyl solvents are substantially soluble in water, and water is substantially soluble in those solvents. RPX 3986; Taber, Tr. 2068.

FF CP 78. Acetone is infinitely soluble in water, and water is infinitely soluble in acetone. RPX 3986

FF CP 79. Methyl acetate is very soluble in water (approximately 23%), and water is very soluble in methyl acetate. RPX 3986

FF CP 80. Ethyl acetate is soluble in water at 2.94%, and water is soluble in ethyl acetate at 8.08%. RPX 3986

FF CP 81. Toluene is soluble in water at 0.052% and water is soluble in toluene at 0.033%. RPX 3986

FF CP 82. The solubility of water in the "wet toluene" used in the Profarmaco process is .03%. Taber, Tr. 2068.

FF CP 83. It is "well-known" that water is immiscible in toluene. Taylor, Tr. 2607.

FF CP 84. The least soluble of the '035 carbonyl solvents (ethyl acetate) is more than 50 times more soluble in water than toluene, and water is more than 200 times more soluble in ethyl acetate than in toluene. RPX 3986.

Water Can Solvate Inorganic Bases

FF CP 85. The solubility of water in the '035 carbonyl solvents, and vice versa, contributes to the ability of the '035 carbonyl solvents to solvate (or solubilize) the potassium bases disclosed in the '035 patent. Taber, Tr. 2145-46.

FF CP 86. One of ordinary skill in the art in 1981 would have known that the solubility of potassium salts in acetone would be enhanced by the addition of water. Taylor. Tr. 2606.

FF CP 87. Water stabilizes and thus makes more soluble negatively charged hydroxide and carbonate ions ("anions") in a reaction solution. RPX 3994; Taber, Tr. 2057-58.

The '035 Carbonyl Solvents Are Both Hydrophilic and Lipophilic Whereas Toluene Is Only Lipophilic

FF CP 88. The '035 carbonyl solvents possess both hydrophilic (water-loving) and lipophilic (oil-loving) properties. RPX 3993; Taber, Tr. 2058; 2068-69.

FF CP 89. Because the '035 carbonyl solvents have both hydrophilic and lipophilic properties, they are able to bring together in solution TZP, the inorganic base, and DMC (in the form of aziridinium). Taber, Tr. 2146.

FF CP 90. Because the '035 carbonyl solvents have both hydrophilic and lipophilic properties, the TZP, inorganic base, and DMC all dissolve in the organic-aqueous phase surrounding the inorganic base particles. Taber, Tr. 2083, 2146.

FF CP 91. Toluene has strongly lipophilic properties with little or no hydrophilic properties. RX 3993; Taber, Tr. 2069, 2077, 2146.

FF CP 92. Because Toluene has very little hydrophilic properties, most water included in the Profarmaco process is associated with the surface of the sodium carbonate base particle. Taber, Tr. 2146.

b. Bases

Sodium and Potassium Bases Are Not Interchangeable in the '035 Process, but Are Interchangeable in Profarmaco's Process

FF CP 93. Sodium carbonate is not equivalent to the potassium bases claimed in claim 1 of the '035 patent. Taber, Tr. 2150.

FF CP 94. The carbonyl containing solvents of the '035 patent are known to be able to solvate at least to some degree potassium. This same phenomenon is not known, however, with sodium, at least not to the same degree. Thus, especially given the teachings of the '035 patent, a person skilled in the art at the time of the alleged '035 invention would have believed that the specific carbonyl containing solvents of the '035 patent were linked with and were capable of providing some solubility only to potassium hydroxide and potassium carbonate. Taylor, Tr. 2604-05.

FF CP 95. Potassium salts are generally more soluble in solvating organic solvents than are sodium salts. Gokel, Tr. 844; Taylor, Tr. 2604-05.

FF CP 96. The sodium cation is more charge dense than the potassium cation. Gokel, Tr. 844.

FF CP 97. Whereas sodium carbonate does not work in the same way as the potassium bases in the '035 patent, sodium carbonate would work in the same way as potassium carbonate in the Profarmaco process. This is because sodium and potassium bases are often interchangeable when dealing with reaction solutions containing pure water, as in the aqueous phase surrounding the inorganic base particle in the Profarmaco process. Taber, Tr. 2146-47.

FF CP 98. Potassium salts and sodium salts are interchangeable in aqueous systems. Taber, Tr. 2117-18.

c. Reaction Mechanisms

The Profarmaco and '035 Processes Operate with Substantially Different Reaction Mechanisms

FF CP 99. The Profarmaco process proceeds with a different mechanism than does the '035 process. Taber, Tr. 2111-12.

FF CP 100. The '035 process is one in which the inorganic base particles (potassium base particles) are surrounded by a solvent-water mixture, wherein the concentration of water is greatest at the surface of the particle and decreases with distance from the particle. Some water is dissolved in the bulk organic phase. Taber, Tr. 2069-71; Gokel, Tr. 705.

FF CP 101. Complainants' expert, Dr. Gokel, has carried out no experiments and is unaware of any experiments carried out by others, comparing a surface solvent

phase formed in the '035 process with a surface solvent phase formed in any of the Respondents' processes. Gokel, Tr. 1053.

FF CP 102. Dr. Baldwin would expect to find more dissolved base in the solvent system of the '035 process than he would in the toluene phase of the Profarmaco process. RX 3048C.

FF CP 103. The pH of the carbonate buffer contained in the aqueous phase of the Profarmaco process is the same, whether sodium carbonate or potassium carbonate is used as the base. Because a dramatic difference is obtained in the '035 process when using a sodium base instead of a potassium base, this indicates that the '035 reaction system is a mixed solvent system, comprising water, organic solvents and potassium base. This mixed solvent system is further evidenced by the knowledge that potassium bases are more soluble than sodium bases in the '035 carbonyl solvents, due to the ability of the carbonyl solvents to solvate potassium ions more efficiently than sodium ions. Taber, Tr. 2147.

FF CP 104. The ratio of water to organic solvent in the '035 process is a gradient or continuum extending outward from the solid base particles of the '035 patent. Taber, Tr. 2069-71. In the '035 system, there exists a "phase boundary" between the ethyl acetate and water phases "which is on the ethyl acetate side more like ethyl acetate; on the water side, more like water. And in the middle there is a progression from one to the other. Gokel, Tr. 705.

FF CP 105. Complainants' expert Dr. Gokel "would certainly expect" that the difference between toluene and

ethyl acetate would alter the phase boundary present in the respective systems. Gokel, Tr. 707.

FF CP 106. The TZP in the '035 process is deprotonated by carbonate or hydroxide ions and the resulting amide anion reacts with the aziridinium ion to yield the alkylated product. Taber, Tr. 2074-75.

FF CP 107. No direct experimental evidence exists that the claimed N-alkylation process of the '035 patent using potassium carbonate as a base is hydroxide-mediated. Gokel, Tr. 1028. If anything, there are indications that it is not hydroxide-mediated. Taylor, Tr. 2674.

FF CP 108. The particular base-solvent combinations of the '035 patent result in the reactants coming together in solution and thus allow the reaction to proceed at relatively low temperatures with good yields. Kende, Tr. 1194.

FF CP 109. Complainants' expert, Dr. Gokel, was unsure whether the actual alkylating agent in either the Profarmaco or the '035 processes is the aziridinium ion. Specifically, the only thing Dr. Gokel knows is that in both reactions some aziridinium ion is formed, but he does not know whether the aziridinium ion is the actual alkylating agent or not. Although he "think[s], it is reasonable that it could be, . . . [he] can't rule out the other possibility." That the alkylation of TZP occurs predominately through the aziridinium ion would be a "guess" to Dr. Gokel. Gokel, Tr. 849-51.

FF CP 110. Dr. Gokel also agreed that the aziridinium ion would be likely involved in the '257 process, in addition to its likely involvement in both the '035 and Profarmaco processes. Gokel, Tr. 850-51.

FF CP 111. Dr. Baldwin's labeling experiments in JEB1-JEB4 do not prove that the aziridinium ion is the alkylating species. RX 3963; RX 4038C.

FF CP 112. Profarmaco's expert testified that in the Profarmaco reaction, the aziridinium ion acts as a phase transfer agent between the thin water layer surrounding the inorganic base particle and the bulk toluene phase. Taber, Tr. 2081, 2109-12; RPX 4000, 4001.

Substantially Lower Amounts of Water Are Present in the Profarmaco Process

FF CP 113. In the Profarmaco process, the amounts of water present are much smaller than the amounts of water present in the '035 process. Specifically, in Example 3 of the '035 patent, the amount of water associated with potassium carbonate is about 1.1 moles of water per mole of potassium carbonate. RX 1688 (Liotta Dep. Tr. 977-78). In contrast, in the Profarmaco process wherein the water concentration of the water-extracted toluene is [C]%, the molar ratio of water to sodium carbonate is about [C]% or [C] times less than in the '035 process. RX 1688.

FF CP 114. The small amount of dissolved water in the toluene of the Profarmaco process exists in aggregates of molecules. Taber, Tr. 2077; RPX 4000.

FF CP 115. The minuscule amounts of water in the toluene associate with the surface of the sodium carbonate base in the Profarmaco process, whereas in the process of the '035 patent significant amounts of water are dissolved in the carbonyl solvent and the water participates in the solvation and dissolution of the inorganic potassium base. RPX 4000; Taber, Tr. 2069-71, 2076-78.

FF CP 116. No mention is made of azeotropic removal of water in any of the examples of the '035 patent. Instead, the '035 patent teaches in the examples that the reaction is carried out under reflux conditions, meaning that the vapors of solvent released from the reaction mixture during boiling are condensed to a liquid in a reflux condenser and returned to the reaction vessel. Gokel, Tr. 904-06.

The Profarmaco Process Is More Like the '257 Process Than the '035 Process

FF CP 117. The Profarmaco process is much more like the '257 process than the '035 process because where reversible deprotonation of the TZP starting material occurs in the '035 process, the TZP starting material in the Profarmaco process is directly alkylated after deprotonation occurs. Thus, no equilibrium (or reversibility) exists in the Profarmaco process between the TZP starting material and its anion. Taber, Tr. 2112-14; RPX 4001.

More Energy Is Required to Carry Out Profarmaco Process

FF CP 118. A higher amount of energy is required for the reaction occurring in the Profarmaco process than for

the reaction occurring in the process of the '035 patent, as reflected by the higher reaction temperatures required for obtaining good yields in the Profarmaco process. Taber, Tr. 2109.

FF CP 119. The Profarmaco process is carried out at a temperature of [C] °[C] versus 77°[C] or less in the '035 process. CX 1; Piselli, Tr. 1987.

Evolution of Carbon Dioxide Occurs in the Profarmaco Process, But Not in the '035 Process

FF CP 120. Because of the higher reaction temperatures necessary to carry out the Profarmaco process, carbon dioxide is evolved during the Profarmaco process, thereby also producing sodium hydroxide. Taber, Tr. 2088.

FF CP 121. Nothing in the '035 patent indicates that carbon dioxide is evolved during the '035 process. Taber, Tr. 2088; Gokel, Tr. 1043-1044.

FF CP 122. The fact that the evolution of carbon dioxide in the Profarmaco process coincides with the production of the product indicates that the hydroxide ion formation, which occurs simultaneously with carbon dioxide evolution, is important to the Profarmaco process. Taber, Tr. 2089.

Different pH Levels Exist in Profarmaco and '035 Processes

FF CP 123. While the pH in the '035 process drops from an initial pH of 11.5 to 8.5, the pH in the Profarmaco

process is maintained at a minimum level of 11.5. Taber, Tr. 2088-89.

FF CP 124. One pH interval level represents a difference in hydroxide ion concentration of a factor of 10. Thus, there is 1000 times more hydroxide ion present in the Profarmaco process than in the '035 process. Taber, Tr. 2089.

FF CP 125. The Profarmaco process operates at a much higher pH level than the process of the '035 patent, due to the higher hydroxide ion concentration and significantly lower amount of water present in the Profarmaco process. Taber, Tr. 2089-90.

d. Experimental Evidence Demonstrates That the Profarmaco Process Works in A Substantially Different Way Than the '035 Process

FF CP 126. At least four different sets of experiments have been made of record in the present investigation demonstrating that when the solvent toluene is substituted for the '035 carbonyl solvents in the '035 process the reaction proceeds very differently: (1) the experiments underlying the EPO Comparative Test Report submitted by Tanabe during the prosecution of the European application corresponding to the '035 patent; (2) experiments conducted by Tanabe scientists in the early 1980's; (3) experiments conducted by complainants' expert Dr. Baldwin; and (4) experiments conducted by Profarmaco. RX 3929, 3494, 3963, 3936; Taber, Tr. 2120-23, 2131-2145.

FF CP 127. At least four different sets of experimental data demonstrate that sodium carbonate reacts quite differently than potassium carbonate in the '035 process: (1) the EPO Comparative Test Report submitted by Tanabe during the prosecution of the European application corresponding to the '035 patent; (2) research reports by the '035 inventors; (3) experimental tests by complainants' expert Dr. Baldwin; and (4) experiments conducted by Profarmaco. RX 3929, 3361, 3963, 3936; Taber, Tr. 2119-23, 2131-2145.

Comparative Test Report

FF CP 128. In Experiment No. 1 of Table 1, a yield of 86.2% was reported when using potassium hydroxide and acetone at a reaction temperature of 50°[C] for a reaction period of 7 hours. RX 3929C. The reaction temperature of 50-60°[C] was within the range described in the '035 patent specification. RX 3048C.

FF CP 129. In Experiment No. 2 of Table 1, a yield of 94.5% was reported when using potassium carbonate and acetone under reflux conditions for a reaction period of 9 hours. RX 3929C.

FF CP 130. In experiment No. 3 of Table 1, a yield of 90.2% was reported when using potassium carbonate and ethyl acetate under reflux conditions for a reaction period of 23 hours. RX 3929C.

FF CP 131. In Experiment No. 4 of Table 1, a yield of 90.7% was reported when using potassium carbonate and acetone/water under reflux conditions for a reaction period of 3 hours. RX 3929C.

FF CP 132. In Experiment No. 5 of Table 1, a yield of 92.7% was reported when using potassium carbonate and ethyl acetate/water under reflux conditions for a reaction period of 6 hours. RX 3929C.

FF CP 133. In Experiment No. 6 of Table 1, a yield of 87.3% was obtained when using potassium carbonate and methyl acetate/water under reflux conditions for a reaction period of 30 hours. RX 3929C.

FF CP 134. The base and solvent systems, reactions temperatures, reaction times and yields obtained in Experiment Nos. 1-6 in Table 1 of the EPO Comparative Test Report correspond with the bases and solvents, reaction conditions and yields obtained in Examples 1, 4, 5, 2, 3 and 7, respectively, of the '035 patent. CX 1; RX 3929-C.

FF CP 135. In Experiment No. 8 of Table 1, the yield of product was reported as "no reaction" when potassium hydroxide and toluene were used at a reaction temperature of 50-60°[C] for a reaction period of 7 hours. RX 3929C. The reaction temperature of 50-60°[C] was within the range described in the '035 patent. RX 3048C.

FF CP 136. In Experiment No. 11 of Table 1, a yield of 10% was reported when using sodium hydroxide and acetone under reflux conditions for a reaction period of 15 to 20 hours. RX 3929C.

FF CP 137. In Experiment No. 12 of Table 1, the yield of product was reported as "no reaction" when sodium carbonate and acetone were used under reflux conditions for a reaction period of 15 to 20 hours. RX 3929C.

FF CP 138. Where "no reaction" is reported in Experiments 8 and 12 of the Comparative Test Report, Tanabe

did not necessarily mean zero yield but rather meant a poor yield. Taber, Tr. 2281.

FF CP 139. Complainants' expert, Dr. Gokel, provided as an explanation for why a 86.2% yield was obtained in Experiment No. 1 (KOH/Acetone) of Table 1, whereas only a 10% yield was obtained in Experiment No. 11 (NaOH/Acetone) of Table 1, was that "[i]t can be explained by the fact this is sodium hydroxide and that's potassium hydroxide. . . . " Another possible explanation for why different yields were obtained in Experiments Nos. 1 and 11 is that in a theoretical sense there exists a difference in the solubilities of potassium hydroxide and sodium hydroxide, which thus could account for the differences in the reaction yields obtained. Dr. Gokel recognized this to be a "well-known phenomenon." Gokel, Tr. 845-47.

Experiments Performed by Tanabe Scientists Toluene Did Not Work in '035 Process

FF CP 140. In a Tanabe technology department report, dated October 1981 (approximately two months prior to the December 1981 date of the Japanese priority patent application upon which the '035 patent is based), Tanabe scientists reported that the N-alkylation of TZP at a reaction temperature of [C] °[C] using [C] as the base and [C] as the solvent did not work. Tanabe repeated the reaction several times, varying the reaction temperature and amount of water added, but were unable to obtain an appreciable product. Taber, Tr. 2136-37; Gokel. Tr. 779-84-RX 3494.

FF CP 141. Dr. Gaino, one of the co-inventors named on the face of the '035 patent, reported in his notebook that N-alkylating TZP using [C] as the base and [C] as the solvent failed to work. Taber, Tr. 2138-39; RX 3368C.

FF CP 142. The Tanabe research reports reflect the Tanabe scientists' finding that toluene is not a useful solvent for the '035 process. Taber, Tr. 2139.

Sodium Carbonate Did Not Work in the '035 Process

FF CP 143. Tanabe performed experiments about three months prior to the December 1981 date of the Japanese priority patent application upon which the '035 patent is based wherein [C] and [C] were substituted for [C] as the base for N-alkylating TZP in [C] . When using either [C] or [C] , tanabe scientists were unable to make the N-alkylation reaction work. The experiment using sodium carbonate and acetone corresponded with Experiment No. 12 in Table 1 of the European Comparative Test Report using sodium carbonate and acetone wherein "no reaction" is reported. Thus, Experiment 12 may be based on this test. RX 3362C, RX 3361C; Taber, Tr. 2123, 2131-35.

FF CP 144. Tanabe Research Reports reflect the finding of Tanabe scientists that sodium carbonate is not useful as a base in the '035 process. Taber, Tr. 2139.

Experiments Performed by Complainants' Expert, Dr. Baldwin, During the Investigation

FF CP 145. Experiments carried out by Complainant's expert Dr. Baldwin demonstrate that toluene does not

work as a solvent in the '035 process. Taber, Tr. 2143-44; RX 3963, RPX 3991C.

FF CP 146. Experiments carried out by Complainant's expert Dr. Baldwin demonstrate that sodium carbonate does not work efficiently as a base in the '035 process, as that process is taught in the patent's examples. Taber, Tr. 2143-2144; RX 3963, RPX 3991C.

FF CP 147. In Experiment JEB15, which was designed to simulate a process of the '035 patent in which toluene was interchanged for a solvent of the '035 patent, a yield of 24% was obtained when N-alkylating TZP with potassium hydroxide as the base and toluene as the solvent at a reaction temperature of 111°[C]. RX 3963; RX 3048C.

FF CP 148. In Experiment JEB16, which was designed to simulate a process of the '035 patent in which toluene was interchanged for a solvent of the '035 patent, a yield of 56% was obtained when N-alkylating TZP with potassium carbonate as the base and toluene as the solvent at a reaction temperature of 111°[C]. RX 3963; RX 3048C.

FF CP 149. In Experiment JEB17, the yield of product obtained dropped from 90.7% to 35% when sodium carbonate was substituted for potassium carbonate under some reaction conditions of Example 2 of the '035 patent. RX 3963; RPX 3991C.

FF CP 150. In Experiment JEB18, the yield of product obtained dropped from 92.7% to 65% when sodium carbonate was substituted for potassium carbonate under

some reaction conditions of Example 3 of the '035 patent. RX 3963; RPX 3991C.

FF CP 151. In Experiment JEB19, the yield of product obtained dropped from 90.7% to 10% when sodium carbonate was substituted for potassium carbonate under some reaction conditions of Example 2 of the '035 patent. RX 3963; RPX 3991C.

FF CP 152. In Experiment JEB20, a yield of 97% was obtained when sodium carbonate was substituted for potassium carbonate under some reaction conditions of Example 3 of the '035 patent, but only after heating the reaction mixture at reflux temperature for 23 hours (almost 4 times the reaction time in Example 3). RX 3963; RPX 3991C.

FF CP 153. Experiment No. 12 in Table 1 of the Comparative Test Report, in which "no reaction" was reported for an N-alkylation reaction using sodium carbonate and acetone, is consistent with the 10% yield that the complainants' expert Dr. Baldwin obtained in JEB 19, wherein sodium carbonate and acetone also were used. Taber, Tr. 2281.

FF CP 154. Experiment No. 8 in Table 1 of the Comparative Test Report, in which "no reaction" was reported for an N-alkylation reaction using potassium hydroxide and toluene, is consistent with the 24% yield that the complainants' expert Dr. Baldwin obtained in JEB 15, wherein potassium hydroxide and toluene also were used. Taber, Tr. 2281.

FF CP 155. Dr. Baldwin's experiments also demonstrated the importance of water removal during the Profarmaco process. RPX 3992; RX 3963.

FF CP 156. In Experiment JEB2 (which sought to mimic the Profarmaco process), Dr. Baldwin's assistants failed to follow his instruction that steps be taken to remove water during the reaction. RX 4038C; Gokel, Tr. 866-67.

FF CP 157. Without taking steps to remove water in JEB2, a yield of only 32% was obtained. RX 3963.

FF CP 158. When Dr. Baldwin repeated Experiments JEB2 with azeotropic water removal, the yield increased from 32% to 98%. RX 3963.

FF CP 159. Complainants' expert, Dr. Gokel, agreed that "an effort was made to remove water" during Dr. Baldwin's repeat of JEB2, including transferring the reaction mixture to a clean Wheaton vile after the neutralization step, as well as using a heat gun to heat the distillation head to ensure that any water adhering to its walls was driven over into the condenser. In addition, a clean condenser was attached to the reaction system prior to completing the reaction. The effort made to remove water in the repeat of Experiment JEB2 was consistent with Profarmaco's effort to remove water during its process by azeotropic distillation. Gokel, Tr. 867-69.

FF CP 160. No attempt also was made to remove water azeotropically during Experiments JEB 15 and JEB 16. Gokel, Tr. 801; RX 3048C.

FF CP 161. Complainants' expert, Dr. Gokel, had no ideal whether Dr. Baldwin's Experiment Nos. JEB1-JEB20

had been optimized; in other words, they may have been or they may not have been. Gokel, Tr. 616-617.

FF CP 162. If Dr. Baldwin's experiments were not already optimized, they could have been optimized if complainants' counsel chose to have it done. Gokel, Tr. 1113-15.

Experiments Performed by Profarmaco During Investigation

FF CP 163. During the course of this investigation, Dr. Piselli of Profarmaco conducted certain experiments. Those experiments are summarized at page 703 of RX 3936. Trial Tr. at 1987-88.

FF CP 164. In Experiments 1-3, Dr. Piselli repeated Example 3 of the '035 process. These experiments were run in triplicate. Piselli, Tr. 1988; RX 3936.

FF CP 165. The yields obtained by Dr. Piselli in these three repetitions of Example 3 of the '035 patent were virtually identical to the yield indicated in the '035 patent itself. Similarly, the product produced, based on TLC analysis and melting point range, appears to be identical to that indicated in Example 3 of the '035 patent. Piselli, Tr. 1988; RX 3936; CX 1.

FF CP 166. In Experiments 4-6, Dr. Piselli used Example 3 of the '035 patent as a starting point for three experiments, in which he substituted sodium carbonate for potassium carbonate. Dr. Piselli ascertained that after a period of time that was slightly longer than that specified in Example 3 of the '035 patent, each of the three

experiments provided a low yield. Piselli, Tr. 1989-1990; RX 3936.

FF CP 167. In Experiment 4, Dr. Piselli therefore extended the reaction time to 15 hours, and in Experiment 6 extended the reaction time to 30 hours and changed a number of other factors. In each instance, the yield remained low. Piselli, Tr. 1989; RX 3936.

FF CP 168. Also, in Experiments 5 and 6, the purity of the product obtained was poor, as characterized by a "NEG" indication in the "Purity by TLC" column. RX 3936 at 703.

FF CP 169. Similarly, the melting points of the product obtained in Experiments 5 and 6 were significantly lower than the melting range for the product obtained by a simple replication of the Example 3 of the '035 patent. Piselli, Tr. 1988-1990; RX 3936 at 703.

FF CP 170. With respect to Experiments 4-6, Dr. Piselli testified that the yields reflected in those experiments "is not a process. It's something that should be abandoned." Piselli, Tr. 1990.

FF CP 171. In Experiments 7 and 8, Dr. Piselli replicated Example 4 of the '035 patent. Piselli, Tr. 1990; RX 3936.

FF CP 172. The yields and quality obtained in Experiments 7 and 8 compare favorably with the yields and quality reflected in Example 4 of the '035 patent. Piselli, Tr. 1990-1991; RX 3996 at 703.

FF CP 173. In Experiments 10 and 11, Dr. Piselli replicated Example 4 of the '035 patent, except that he

substituted sodium carbonate for potassium carbonate. Piselli, Tr. 1991; RX 3936.

FF CP 174. Experiments 10 and 11 produced a low yield and a poor quality product, as reflected by the "neg" comment in the purity by TLC column. These results were not improved by continuing the reaction for 18 hours. Piselli, Tr. 1991; RX 3936 at 703.

FF CP 175. Experiments 4-6 and 10-11 demonstrate that sodium carbonate is not a useful base in the '035 process. Taber, Tr. 2142.

FF CP 176. In Experiment 15, Dr. Piselli replicated Example 3 of the '035 patent except that he substituted toluene as the solvent in the place of ethyl acetate. Dr. Piselli used the reflux temperature of ethyl acetate, as used in the patent example. The yield was extremely low and the product was not pure. Piselli, Tr. 1991-1992, 2031; RX 3936 at 703.

FF CP 177. In Experiment 16, Dr. Piselli replicated Example 3 of the '035 patent except that he substituted toluene for acetone. There was no yield in this reaction at all. Dr. Piselli used the boiling temperature of acetone. Piselli, Tr. 1992, 2031; RX 3936 at 703.

Optimization Defined

FF CP 178. Optimization is not the same thing as experimentation. A process is optimized only after it has been found to be a "consistent" process, specifically a process from which "a well-defined product with a well-defined yield" is obtained. It is only at this point in time

that "technological optimization" (*i.e.*, trying "small variations in the operating parameters") of a process is conducted. For example, if an experiment using the same reactants and reaction conditioner was repeated ten times, any variation in yield would be minimal. Piselli, Tr. 2017-18, 2021.

FF CP 197. Dr. Piselli testified that one could not "optimize" the Profarmaco experiments: "Optimization is one thing, the process is another. You optimize a process that has a certain consistency and is valid, but if the process doesn't exist, you don't optimize it." Piselli, Tr. 1990.

e. The Profarmaco Process Also Performs A Substantially Different Function and Achieves A Substantially Different Result Than the '035 Process

FF CP 180. Because claim 1 of the '035 patent does not include a recovery step, the product of claim 1 is N-alkylated TZP in a reaction mixture containing water, a polar, water-miscible carbonyl solvent and various salts. CX 1; Taber, Tr. 2183.

FF CP 181. The Profarmaco process produces a solution of N-alkylated TZP in toluene taber, TR. 2183-2184. FFCP 182. The examples of the '035 patent teach that the N-alkylated TZP obtained as the product of claim 1 of the '035 patent must be isolated, purified, and transferred to another reaction vessel before the manufacture of diltiazem can proceed. CX 1; Piselli, Tr. 1987.

FF CP 183. The product of Profarmaco's sodium carbonate/toluene N-alkylation process provides commercial advantages, for example, convenience, unobtainable using the product of the N-alkylation process claimed in the claim 1 of the '035 patent. Taber, Tr. 2183-2185.

FF CP 184. Because toluene is immiscible with water, the solution of N-alkylatedTZP in toluene produced from the N-alkylation step of the Profarmaco process can be directly washed with water to remove byproducts and unreacted DMC, leaving behind a solution in which one can directly carry out the subsequent acetylation reaction. Taber, Tr. 2185.

FF CP 185. The function of the process of claim 1 of the '035 patent is to produce an organic reaction mixture containing N-alkylated TZP in a carbonyl solvent-water mixture. This product will contain water, dissolved base and salts along with alkylated TZP. To utilize the solubilized N-alkylated TZP, the reaction mixture must be (i) extracted, (ii) washed, (iii) filtered, (iv) concentrated, (v) redissolved, and (vi) transferred to another reactor prior to the subsequently applied steps, including, *inter alia*, the acetylation and salt-forming steps. RX 3348; Taber, Tr. 2183; Piselli, Tr. 1987.

B. The Abic Process Does Not Infringe Claim 1 of the '035 Patent

1. The Abic Process Is Not Equivalent to Any Process Disclosed Or Claimed By The '035 Patent

FF CA 1. The Abic process does not employ either of the two bases or either of the two organic solvents or any

of the five specific base-solvent combinations identified in the '035 patent. *See* RX 1194; RX 1195.

FF CA 2. Abic's commercial process uses barium hydroxide octahydrate as a base, a biphasic solvent system of methylene chloride and water, and triethylbenzylammonium chloride (TEBA) and is similar to the process described in example 4 of its United States Patent No. 4,466,995 ("the '995 patent"). RX 1701C.

FF CA 3. All the processes used by Abic to manufacture diltiazem hydrochloride were disclosed in the Abic DMF. [C]. RX 1701.

The Bases Are Not Equivalent

FF CA 4. Abic's base is barium hydroxide octahydrate, and not potassium hydroxide or potassium carbonate. RX 1194; Taylor Tr. 2638; RX 1701C.

FF CA 5. The '035 patent does not disclose or suggest barium hydroxide to a person of ordinary skill. Taylor Tr. 2609.

FF CA 6. Barium is an alkaline earth metal, and as such forms divalent cations. Taylor Tr. 2609.

FF CA 7. Among other things, barium hydroxide is less soluble than potassium hydroxide in carbonyl solvents such as acetone and lower alkyl acetates. Taylor Tr. 2610.

FF CA 8. If one of ordinary skill in the art were investigating the interchangeability of other bases with the potassium bases of the '035 patent, one would likely first try sodium hydroxide (NaOH) because sodium

hydroxide is more common and substantially less expensive than potassium hydroxide. Taylor Tr. 2626.

FF CA 9. Tanabe tried and abandoned sodium hydroxide in combination with DMSO. RX 1589C.

FF CA 10. As is shown by the Comparative Test Report, Tanabe did try the base/solvent combination of sodium hydroxide and acetone, and concluded that it was not part of the method of the invention of the '035 patent. Tr. 2636; RPX 1146; RX 1096; RX 1344; RX 3225.

FF CA 11. Barium hydroxide would be expected to be less effective than sodium hydroxide in the '035 process because barium is even less soluble than sodium in the carbonyl solvents acetone or ethyl acetate of the '035 patent. Taylor Tr. 2627.

FF CA 12. Consequently, if sodium hydroxide were found to be not as good as potassium hydroxide, one of ordinary skill in the art would not be led to try barium hydroxide, since barium hydroxide would be expected to be even worse in the '035 process, which discloses solvation of the solid base in a carbonyl solvent. Taylor Tr. 2627.

FF CA 13. Accordingly, one of ordinary skill in the art, knowing that even sodium hydroxide was not interchangeable with potassium hydroxide would not have expected that barium hydroxide would be interchangeable with potassium hydroxide or potassium carbonate. Taylor Tr. 2609-10.

The Organic Solvents Are Not Equivalent

FF CA 14. The organic solvent in Abic's process is methylene chloride. RX 1195; Taylor Tr. 2641; RX 1701C.

FF CA 15. The '035 patent does not teach the use of methylene chloride as an oroganic solvent to be used in the N-alkylation of the '035 process. *See* Taylor Tr. 2612.

FF CA 16. The '035 patent disclosed chloroform, a chlorinated hydrocarbon like methylene chloride, but did not disclose its use or the use of any other chlorinated hydrocarbon solvent in its N-alkylation process. CX 1; Gokel Tr. 769-70.

FF CA 17. Acetone is a ketone. Taylor Tr. 2621.

FF CA 18. One of ordinary skill in the art looking to investigate the scope of potentially interchangeable solvents to replace acetone in the '035 process would have looked for solvents which shared the important structural and functional characteristics of the carbonyl solvents of the '035 patent. *i.e.*, would have looked at oxygen-containing, cation-solvating, water-miscible solvents. Taylor Tr. 2624.

FF CA 19. Some common solvents which one might have investigated include methyl ethyl ketone, dioxane, methanol, and DMSO. Taylor Tr. 2621-24; RPX 1155.

FF CA 20. Methylene chloride would not be one of the solvents one would first try since it does not solvate cations well, has no oxygen atoms to act as donors, and is nearly totally immiscible with water. Taylor Tr. 2624.

FF CA 21. If solvents such as dioxane, methanol, and methyl ethyl ketone were not as effective as acetone in a

reaction, one would not be led to try methylene chloride, since that would be going in the "wrong direction," to even more inferior water-immiscible solvents. Taylor Tr. 2624-25.

Tanabe Tried to Extend the Scope of It's Invention in 1981 and Failed

FF CA 22. Tanabe tried sodium carbonate instead of potassium carbonate, but it did not work as well as the '035 bases. RX 3368; Taber Tr. 2134-36.

FF CA 23. Tanabe tried structurally and functionally similar solvents, such as dioxane, methyl ethyl ketone, methanol, and DEMSO, and they didn't work as well as the '035 solvents. RX 3361, Gokel Tr. 928-31; RX 2046; Gokel Tr. 676-79; RX 3368; Taber Tr. 2138; RX 1272C; Taylor Tr. 2629-31.

FF CA 24. In fact, Tanabe tested and abandoned the base-solvent combination of potassium carbonate-methyl ethyl ketone (the combination currently employed by fermiomion) because Tanabe could not get that combination to work. Taylor Tr. 2629; Gokel Tr. 676-79; RPX-10161a; and RX-2046.

FF CA 25. Tanabe did not try barium hydroxide as a base, methylene chloride as a solvent, or the combination of barium hydroxide and methylene chloride. *See* Taylor Tr. 2633; RX 1703.

The Liquid-Solid Process of the '035 Patent and the Abic Liquid-Liquid Process Are Not Equivalent

FF CA 26. Each of the organic solvent-water mixtures of the '035 patent forms a single liquid phase, *i.e.*, it is a solution of water in the acetone or lower alkyl acetate organic solvent. Taylor 1804, 2666-68.

FF CA 27. Abic's solvent system is a biphasic solvent system – it consists of two distinct liquid phases – methylene chloride and water. RX 1195; Liotta Tr. 1804-05; Taylor Tr. 2664, 2666-67.

FF CA 28. There is no solid phase present in the Abic process. Schwartz Tr. 2520-21.

FF CA 29. Liquid-liquid phase transfer catalyst processes such as that used by Abic and solid-liquid processes such as those of the'035 patent are not chemically equivalent. Taylor Tr. 2667; RX-3969 at 108.

FF CA 30. Dr. Liotta wrote in his book that, even when a solid-liquid process and a liquid-liquid process are both phase transfer catalyzed, they are by no means equivalent. RX 3969 at 108.

Abic's Process Is Phase Transfer Catalyzed by TEBA

FF CA 31. Dr. Charles Liotta, complainants' expert with respect to infringement of the '035 patent by the Abic process, submitted a declaration in this investigation in which he stated that:

> Convincing evidence has not been presented by Abic to date that (TEBA) is operating as a phase

transfer catalyst in their N-alkylation process step.

RX 1333C, ¶ 6d.

FF CA 32. At his deposition, Dr. Liotta explained how such evidence could be generated:

> Q If I have two experiments, one where I have a phase transfer catalyst present and one where it is exactly the same but I leave out the phase transfer catalyst, and the rate in the one with the phase transfer catalyst is faster than the one without it, does that indicate that a phase transfer catalysis is taking place?
>
> A If you have repeated the experiments so you have reproductibility and stirring speeds are the same in both and everything was the same, the indication is that you have evidence for the operation of phase transfer catalysis.

Liotta Tr. 1832-33.

FF CA 33. Abic carried out a series of such experiments, as described by Dr. Liotta, which are identified as experiments 1, 10, and 14-20 on RPX 1051a. Taylor Tr. 2642-45.

FF CA 34. In experiments 1, 14, 17, 18, the N-alkylation was performed in the presence of TEBA catalyst; experiments 10, 13, 15, 16, 19 and 20 did not use the TEBA phase transfer catalyst. RPX 1051a.

FF CA 35. The TZP and DMC were allowed to react in the methylene chloride-water biphasic solvent system for 1.5, 3, 6, or 12 hours. RPX 1051a.

FF CA 36. Experiments 14 and 17, 15 and 16 are repeats of each other, and the similar results indicate that the results were reproducible. Taylor Tr. 2645-47.

FF CA 37. The stirring speeds were carefully controlled, and were essentially the same in all experiments. Schwartz Tr. 2524, 2532.

FF CA 38. The Abic experiments met the criteria set forth by Dr. Liotta. Taylor Tr. 2650.

FF CA 39. The results were plotted on a graph which shows that the phase-transfer catalyzed reaction was at least twice as fast as the uncatalyzed reaction. Taylor Tr. 2647-49; RPX 1058.

The Abic Process Functions in a Different Way Than the '035 Process

FF CA 40. In the Abic liquid-liquid biphasic solvent process, the TZP and DMC are in the organic phase (the methylene chloride layer), while the barium hydroxide remains dissolved in the aqueous phase. TEBA, the phase transfer catalyst, is soluble in both phases. The aziridinium ion which, as a cation, is insoluble in methylene chloride, remains in the aqueous layer. Taylor, Tr. 2638; RPX 1156.

FF CA 41. The hydroxide ion in the water layer cannot efficiently deprotonate the TZP in the methylene chloride layer, because they are in separate layers, organic and aqueous. The TEBA phase transfer catalyst carries the hydroxide ion as TEBA hydroxide into the methylene chloride layer, where it deprotonates the TZP.

The TZP anion can then react with DMC to N-alkylate the TZP N-aryl amide. Taylor Tr. 2638; RPX 1099.

FF CA 42. The methylene chloride phase has an additional function in the Abic process over and above the function of acetone in the '035 process. Taylor Tr. 2641.

FF CA 43. The water-immiscible solvent methylene chloride keeps the TZP and DMC separate from dissolved aqueous barium hydroxide. Taylor Tr. 2641

FF CA 44. Kugita I discloses that TZP can hydrolyze in the presence of aqueous sodium hydroxide, especially at higher temperatures. RX 3806; Kende Tr. 1452-54.

FF CA 45. Abic's experience with biphasic toluena-aqueous hydroxide processes is in accord; at higher temperatures, hydrolysis of TZP was seen. RX 1007C; Haber Tr. 2417-20.

FF CA 46. In the Abic process, the methylene chloride, operating at 40° C, protects the TZP and DMC from hydrolysis by aqueous barium hydroxide. Taylor Tr. 2641.

FF CA 47. Because there is no aqueous hydroxide in the '035 solid-liquid potassium hydroxide/acetone process, hydrolysis is not a problem in the '035 process. Taylor Tr. 2666; Taber Tr. 2173.

Abic's Process Is Not Equivalent to the Potassium Hydroxide-Acetone Process of the '035 Patent

FF CA 48. Abic's expert compared the potassium hydroxide (KOH)/acetone system of the '035 patent and the barium hydroxide/methylene chloride system of Abic's process. Taylor Tr. 2664-65; RPX 1157.

FF CA 49. The bases and solvents are different. *Id.*

FF CA 50. There is no water in the '035 potassium hydroxide process; thee is a separate aqueous layer in the Abic barium hydroxide process. *Id.*

FF CA 51. There is one solvent phase in the '035 process; there are two solvent phases in the Abic process. *Id.*

FF CA 52. The alkylating agent in the '035 process is aziridinium ion, and is located in the acetone single solvent phase in the '035 process. CPX 14; RPX 1157; Taylor Tr. 2664.

FF CA 53. In Abic's process, the active alkylating agent, DMC itself, is located in the methylene chloride phase. Taylor Tr. 2665.

FF CA 54. In the '035 process, potassium hydroxide is able to deprotonate TZP because it is somewhat soluble in the acetone solvent. In the Abic process, barium hydroxide, which is not soluble in methylene chloride, is able to deprotonate TZP via phase transfer catalysis. Taylor Tr. 2656, 2668.

FF CA 55. The potassium hydroxide in the '035 system and barium hydroxide in Abic's system do not function the same way to deprotonate TZP. Taylor Tr. 2665.

FF CA 56. The organic solvents in the '035 and the Abic processes have different functions: the function of acetone in the '035 process is to solubilize the KOH base in the organic phase; the solvents in Abic's process have the important function of separating the reagents. Taylor Tr. 2665-66.

FF CA 57. The '035 process is a solid-liquid system while the Abic process is a liquid-liquid system. Taylor Tr. 2666.

FF CA 58. The Abic process uses the phase transfer catalyst TEBA, but there is no phase transfer catalyst in the '035 process. Taylor Tr. 2665.

FF CA 59. Solid-liquid phase-transfer-catalyzed systems and liquid-liquid phase transfer catalyzed systems are not regarded as equivalent in the art. Taylor Tr. 2666-67; RX 3969.

FF CA 60. Abic's liquid-liquid phase-transfer-catalyzed system is even less equivalent to a simple solid-liquid system, i.e., a solid-liquid system without a phase transfer catalyst, such as that of the '035 process. Taylor Tr. 2667; RX 3969.

FF CA 61. Phase transfer of the hydroxide ion could be effected by heating Abic's system. Unlike catalysis, which selectively increases the rate of hydroxide ion transfer, heating indiscriminately speeds up everything that is going on, thus increasing the potential for side reactions. Taylor Tr. 2668-69; RX 3969.

FF CA 62. Examples of side reactions which could occur in the Abic system as a result of heating to speed up the reaction are: dimer formation, hydrolysis of DMC, and hydrolysis of TZP. Taylor Tr. 2669-70; RPX 1051a.

FF CA 63. In Abic's process, dimer formation is inhibited by use of a phase transfer catalyst. Taylor Tr. 2669-70; RPX-1051a.

FF CA 64. Use of a phase transfer catalyst in Abic's system also enables a reduction in the volume of solvent used. Taylor Tr. 2670-71; RX-1024.

FF CA 65. The elements of Abic's barium hydroxide process, i.e., the base, the two solvents, the alkylating agent, and the phase transfer catalyst, are not the same as the elements of the potassium hydroxide/acetone base/solvent combination of the '035 patent, and the two processes do not function in the same way and are not equivalent. *See* Taylor Tr. 2672.

FF CA 66. Even if the alkylating agents were the same, and phase transfer catalysis were not taking place, the two processes would still not be equivalent. *See* Taylor Tr. 2672.

FF CA 67. That the '035 process starts with the same substrate, employe the same alkylating agent, and obtains the same product has no bearing on the equivalence of the base/solvent combinations to the claimed process, because the starting material, alkylating agent and the product are the prior art, not the elements of the claimed improvement. *See* Taylor Tr. 2672-73.

The Abic Process System Is Not Equivalent to the Potassium Carbonate/Acetone or Potassium Carbonate/Ethyl Acetate Processes of the '035 Patent

FF CA 68. The Abic process is even less similar to the potassium carbonate/acetone or potassium carbonate/ethyl acetate processes of the '035 patent, because the Abic base, barium hydroxide ($Ba(OH)_2$), is not a carbonate base, but a hydroxide base. RPX 1157; Taylor Tr. 2673.

FF CA 69. The Abic process is not equivalent to the potassium carbonate/acetone or potassium carbonate/lower alkyl acetate processes of the '035 patent because those processes cannot be made to work as they are disclosed by the '035 patent. *See* Taylor Tr. 2675.

FF CA 70. Attempts by Abic to replicate Examples 4 and 5 of the '035 patent (powdery potassium carbonate=acetone and powdery potassium carbonate-ethyl acetate, with no added water) failed. Taylor Tr. 2675; RPX-1051A.

FF CA 71. Abic found that the potassium carbonate/acetone and potassium carbonate/ethyl acetae base/solvent combination is do not work without added water. Taylor Tr. 2676, 2680-81; RX 1272.

FF CA 72. The Tanabe laboratory notebooks produced by Tanabe and in evidence showed that Tanabe knew from experiments conducted in 1981, before it filed its patent application on December 7, 1991, that the potassium carbonate/acetone and potassium carbonate/ethyl acetate combinations did not work consistently without added water. Taylor Tr. 2677; Taber Tr. 2099, 2148.

FF CA 73. Abic's process, which consistently works, is not equivalent to the '035 systems of potassium carbonate/acetone and potassium carbonate/ethyl acetate, which do not work. Taylor Tr. 2678; RX 1272C.

FF CA 74. If, contrary to the evidence, it were assumed that the '035 processes of potassium carbonate/acetone and potassium carbonate/lower alkyl aceate did work, the Abic process would not be equivalent to either process. *See* Taylor Tr. 2673, 2680.

FF CA 75. Barium hydroxide and potassium carbonate bases are different, and are non-equivalent ways of deprotonating TZP, because the deprotonating species is hydroxide (OH^-) in the one case, and carbonate ion (CO_3^-) in the other. Taylor Tr. 2673-74.

FF CA 76. To make the potassium carbonate and barium hydroxide bases seem more similar, complainants have postulated that the potassium carbonate processes are "hydroxide mediated"; that is, that potassium carbonate forms some hydroxide ion, which then deprotonates TZP. CPX 14; Gokel Tr. 709.

FF CA 77. There is no evidence that the potassium carbonate processes of the '035 patent are hydroxide mediated. Taylor Tr. 2674.

FF CA 78. Dr. Kende testified that he didn't know whether the processes were hydroxide mediated or not, and didn't even know how one would carry out an experiment to determine this. Kende Tr. 3415-16.

FF CA 79. Abic's process is not equivalent to the potassium carbonate/acetone combination; and for the additional reasons that these '035 processes employ a different base, and are not hydroxide mediated. *See* Taylor Tr. 2679.

Abic's Process Is Not Equivalent to the Potassium Carbonate/Acetone-Water and Potassium Carbonate/Lower Acetate-Water System of the '035 Patent

FF CA 80. Potassium carbonate processes with added water are similar to the potassium carbonate/acetone of potassium carbonate/ethyl acetate processes of the '035

patent, except that with the small added amount of water they produce satisfactory results. Taylor Tr. 2681-82; RPX 1051A.

FF CA 81. Although there is a small amount of water in the potassium carbonate/acetone-water and potassium carbonate/ethyl acetate-water processes, they are still solid-liquid processes, because the water (a) reacts with potassium carbonate to form solid potassium carbonatesesquihydrate, or (b) dissolves in the acetone or lower alkyl acetate solvent. Taylor Tr. 2682-3; 2687-98.

FF CA 82. For the same reasons that the Abic process is not equivalent to the KOH/ACETONE processes, or the potassium carbonate/acetone and potassium carbonate-lower alkyl acetate processes, it is not equivalent to the potassium carbonate-acetone-water or potassium carbonate-lower alkyl acetate-water processes. Taylor 2681-82.

FF CA 83. Abic repeated Examples 3 and 7 of the '035 patent, with yields similar to those reported by the '035 patent, and observed only one solid phase and one liquid phase. Schwartz Tr. 2513-15; RX 1175; Taylor Tr. 2692-82; RPX1051a.

FF CA 84. Abic also performed some experiments which showed that the '035 solid-liquid processes, even with added water, and the Abic liquid-liquid processes were fundamentally different. RPX 1051a; Taylor Tr. 2682-86.

FF CA 85. Abic performed an experiment repeating Example 3 of the '035 patent (potassium carbonate/ethyl

acetate-water) but in which methylene chloride was substituted for ethyl acetate. After 6 hours (as specified in the '035 example), there was 21.5 percent of unreacted TZP and 77 percent of product. Taylor Tr. 2684; RPX-1051a.

FF CA 86. The yield of '035 Example 3 is reported to be 92.7%. RX 1194.

FF CA 87. The yield of the process is important in determining the equivalence of commercial processes, which require high yields. Gokel Tr. 1116-17.

FF CA 88. Abix performed as identical experiment with the sale difference that a small amount of TEBA phase transfer catalyst was added. After 6 hours, there remained 77 percent of product, but only 2.7 percent of unreacted starting material and a large amount of the dimer side product. Taylor Tr. 2684; RPX1051a.

FF CA 89. Abix also repeated Example 4 of Abic's '995 patent, with and without the TEBA phase transfer catalyst. In Abic's liquid-liquid biphasic solvent process, the results were exactly the reverse, a dimer was formed in the absence of phase transfer catalyst, but no dimer was formed in the presence of the phase transfer catalyst. Taylor Tr. 2685-86; RPX 1051a.

FF CA 90. It is not surprising that the two systems behave in opposite ways, since they are completely different systems. Taylor Tr. 2686.

FF CA 91. Complainants assert that the small amount of water present in these base/solvent combinations of the '035 patent is present as a "surface solvent phase" which complainants attempt to liken to the aqueous

phase of Abic's biphasic solvent process. *See* Taylor Tr. 2698-99.

FF CA 92. Complainants introduced no evidence of such a surface solvent phase under the base-solvent conditions of the '035 patent. See Liotta Tr. 1762-64, and 1779-81.

FF CA 93. The "surface solvent phase" is postulated by complainants to be a very thin layer, approximately 100 angstroms (A) thick, of indeterminate composition associated with the solid. Gokel Tr. 707, 1053.

FF CA 94. It would take 50,000 of the postulated 100 A surface solvent phases laid one on top of the other to make up the thickness of a pencil line. The surface solvent phase would be invisible to the naked eye. Wrighton Tr. 1610.

FF CA 95. Even if there were a surface solvent phase, the two processes would still be non-equivalent, for the reasons set forth above. *See* Taylor Tr. 2698-99.

FF CA 96. Professor Wrighton of M.I.T., an expert on surface chemistry, testified that the term "surface solvent phase" was not customarily used in surface chemistry, and had no recognized meaning. Wrighton Tr. 1608.

FF CA 97. Before this investigation, Dr. Liotta had never used the term "surface solvent phase" in any publication. Liotta Tr. 1749.

FF CA 98. Before this investigation, Dr. Liotta had never called a surface solvent phase a "biphasic solvent system." It appears that he used that terminology as and analogy to Abic's biphasic solvent system. Liotta Tr. 1705-06.

FF CA 99. The postulated surface solvent phase film, of indeterminant composition, and only 1/50,000th of the thickness of a pencil line, is not the chemical equivalent of the aqueous phase of the Abic methylene chloride-water biphasic solvent system. Taylor Tr. 2700.

FF CA 100. Dr. Liotta performed experiments attempting to prove the presence of a surface solvent phase when water was added to a mixture of potassium carbonate and ethyl acetate. Liotta Tr. 1812-13; CX 636.

FF CA 101. Dr. Liotta's experiments established that the potassium carbonate and water did not form a "surface solvent phase", but formed the well known solid compound potassium carbonate sesquihydrate ($K_2CO_3 \cdot 1.5H_2O$). Taylor Tr. 2687-2697.

FF CA 102. Potassium carbonate sesquihydrate is not a surface solvent phase. Gokel Tr. 1052; Wrighton Tr. 1622; Taylor Tr. 2688.

FF CA 103. Abic repeated Dr. Liotta's experiments, and tested the products by differential scanning calorimetry (DSC). RX 1702.

FF CA 104. Dr. Wrighton testified that the DSC results established that when potassium carbonate was treated with water in ethyl acetate as Dr. Liotta had done, the products were potassium carbonate sesquihydrate, or potassium carbonate sesquihydrate with some residual potassium carbonate. Wrighton Tr. 1602-22.

FF CA 105. Dr. Ronald Jenkins of the International Center for Diffraction Data testified as to analyses he had performed on the same material that Dr. Wrighton testified about. Dr. Jenkins concluded that the products were

potassium carbonate sesquihydrate, or potassium carbonate sesquihydrate, with some residual potassium carbonate. Jenkins Tr. 2945-2953.

2. Abic Independently Developed Its Own Process – It Did Not Copy the Process of the '035 Patent

Abic's Initial Experiments

FF CA 106. In 1982 Abic decided to market a calcium channel blocker, and chose diltiazem as its goal. Haber Tr. 1401.

FF CA 107. Although thee was no patent on diltiazem in Isreal, Abic sought a license from Tanabe for sale to other countries. Haber Tr. 2402.

FF CA 108. Tanabe refused to license Abic, or to supply raw material. Haber Tr. 2402-2403.

FF CA 109. As a consequence, Abic began research and development of the overall process for synthesizing diltiazem hydrochloride in December 1982 or very early in 1983. Habert Tr. 2402.

FF CA 110. By early 1983, Abic knew of the '257 patent and its foreign counterparts, but not of the '035 patent or any foreign counterpart of it. Haber Tr. 2403-04.

FF CA 111. There are about seven or eight steps in Abic's procedure to manufacture diltiazem hydrochloride, and the N-alkylation is the fifth or sixth step. Haber Tr. 2404.

FF CA 112. Therefore, it wasn't until May of 1983 that Abic had the starting material in hand to enable it to begin working on the N-alkylation step. Haber Tr. 2408.

FF CA 113. Abic's work on the synthesis of diltiazem hydrochloride, particularly the N-alkylation step, is reflected in Abic's internal periodic reports for 1982 and 1983. Haber Tr. 2409-10; RX 1007C; RX 1008C; RX 1009C; RX 1010C; RX 1013C; RX 1015C.

History of Abic Work on N-Alkylation

Date	Event
May 1983	First N-alkylation NaH/DMSO
August 1983	First phase transfer catalyst work KOH + Methylene Chloride + Water + TBABr Fix on methylene chloride as solvent Fix on TEBA as PTC Try NaOH as base
September – November 1983	NaOH + Methylene Chloride + Water + TEBA
December 1983	Try other than alkali metal bases $Mg(OH)_2$ $Ca(OH)_2$ NH_4OH $CaCO_3$ MEt_3 Knowledge of EPO '035 counterpart
February 1984	Test $Ba(OH)_2 \cdot H_2O$

FF CA 114. Based on the literature, Abic believed that alkylating the nitrogen on the seven-membered ring would be a straightforward procedure. Haber Tr. 2406-07.

FF CA 115. Because Abic needed diltiazem precursor for study of the acetylation step, and for further pharmaceutical testing, Abic began alkylating TZP under the conditions already reported in the '257 patent and the Kugita publications, sodium hydride and DMSO. Haber Tr. 2411.

The Early Development of Abic's Phase-Transfer Catalyzed, Methylene-Chloride-Water Processes

FF CA 116. Abic quickly moved away from the sodium hydride-DMSO base-solvent combination by replacing DMSO with DMF. Haber Tr. 2411-12.

FF CA 117. Abic then began to look for alkylation processes which did not employ sodium hydride. Haber Tr. 2412.

FF CA 118. It was known at that time, the summer of 1983, that one could alkylate carbon atoms (C-alkylation) using either harsh conditions or the milder conditions of phase transfer catalysis, in the presence of water, and it was felt that those milder phase transfer catalysis methods could be adapted to the N-alkylation of TZP. Haber Tr. 2412.

FF CA 119. Abic believed that alkylating under milder conditions would minimize the possibility of side reactions. Haber Tr. 2412-13.

FF CA 120. Although there is a large amount of water present in classical phase transfer conditions, Abic

was not concerned with potential hydrolysis of the TZP. Haber Tr. 2413-14.

FF CA 121. Similarly, Abic was not concerned with the potential retro-Michael reactions under phase transfer catalyzed conditions because of the particular structure of the TZP molecule. Haber Tr. 2414-15.

FF CA 122. Because Tanabe had not observed O-alkylation at the 3-hydroxyl group of TZP under the harsher conditions of the '257 patent, Abic was not concerned that such O-alkylation was likely to take place under the milder phase-transfer conditions. Haber Tr. 2415.

FF CA 123. Abic was not concerned about the potential for alkylation at the carbonyl oxygen because in the presence of a base, alkylation occurs almost exclusively at the nitrogen. Haber Tr. 2416.

FF CA 124. Abic was not concerned that DMC would be unstable under Abic's phase transfer conditions because, as with all alkylating agents, conditions can be modified to minimize instability. Haber Tr. 2416-17.

FF CA 125. In August, 1983, Abic tried two phase transfer catalyzed processes, one using potassium hydroxide-methylene chloride-water and the other using potassium hydroxide-toluene-water, both with TEBA bromide as the phase transfer catalyst. Haber Tr. 2413.

FF CA 126. In August, 1983 Abic was not aware of the '035 patent or any of its foreign counterparts. Haber Tr. 2413.

FF CA 127. The phase transfer catalyzed reaction in toluene did not work at low temperatures, and at high

temperatures there was some hydrolysis of the lactam. Haber Tr. 2418-19; RX 1007C.

FF CA 128. However, the phase transfer catalyzed reaction in methylene chloride worked well at low temperature, so hydrolysis which could occur at high temperature was not a problem. Haber Tr. 2418-19; RX 1007C.

FF CA 129. Although Abic tried a number of other solvents, none were as good as methylene chloride, so from August, 1983, Abic concentrated on developing the methylene chloride-water phase transfer catalyzed process. Haber Tr. 2422-23.

FF CA 130. Abic also experimented with several phase transfer catalysts, but rapidly settled on TEBA because it gave the best results. Haber Tr. 2423-24.

FF CA 131. The product of the alkylation using potassium hydroxide as the base was somewhat impure. Haber Tr. 2423-25.

FF CA 132. In August 1983, therefore, Abic tried sodium hydroxide as the base, since it was the most similar base to potassium hydroxide. RX 1008; RPX 1144; Haber Tr. 2424-25.

FF CA 133. Sodium hydroxide gave a purer product, but it still contained about 10% of the unidentified impurity. Haber Tr. 2425.

FF CA 134. Abic continued using sodium hydroxide as a base for two to three months to make precursor for use in studying the subsequent acetylation, hydrochlorination and purification processes. Haber Tr. 2425-26.

Abic's Development of Its Phase-Transfer-Catalyzed Barium Hydroxide-Methylene Chloride-Water Process

FF CA 135. Eventually Abic discovered that the impurity obtained with potassium hydroxide and sodium hydroxide was "dimer", which was formed by an alkylation reaction between the solvent methylene chloride and two molecules of TZP. Haber Tr. 2426.

FF CA 136. Abic also was aware of British Patent No. 1,236,467, a counterpart of the '257 patent, as well as other counterparts, claiming alkylation processes employing alkali metal salts. RX 1010C; RX 1700; Haber Tr. 2432.

FF CA 137. In an effort to avoid the formation of dimer, and in an attempt to develop a process using bases other than alkali metal bases which would not infringe the '257 foreign counterpart process patents, Abic in December, 1983 began experimenting with ammonium hydroxide, magnesium hydroxide and calcium hydroxide. Haber Tr. 2429-31, 2434.

FF CA 138. Abic also apparently became aware in December of 1983, for the first time, of the European patent application that was the counterpart of the '035 patent. Haber Tr. 2429-30.

FF CA 139. Abic was not concerned with potential infringement in Europe, because the European application was restricted to potassium bases, and Abic at the time was using sodium hydroxide. Haber Tr. 2435.

FF CA 140. Ammonium hydroxide and magnesium hydroxide bases did not work in the Abic phase transfer catalyzed methylene chloride-water process. Haber Tr. 2431.

FF CA 141. However, calcium hydroxide in the phase transfer catalyzed methylene chloride-water process gave high purity product without the formation of the unwanted dimer. Haber Tr. 2431-32.

FF CA 142. Neither calcium hydroxide nor calcium carbonate in acetone resulted in N-alkylation. RX 1010C; Haber Tr. 2430-31.

FF CA 143. In February 1984, Abic tested barium hydroxide with its methylene chloride-water-TEBA system and found that barium hydroxide gave good yields, practically no formation of dimer, and fewer side reactions with DMC. Haber Tr. 2436.

FF CA 144. Abic repeated tests of other bases in the methylene chloride-water system with a phase transfer catalyst, and confirmed that potassium hydroxide and potassium carbonate yielded large amounts (20%-30%) of the dimer under those conditions. Haber Tr. 2436-37; RX 1015C.

FF CA 145. For comparative purposes, Abic also tried some of the base-solvent combinations of the EPO 81234 application, but Abic did not pursue those combinations because Abic has a policy of not infringing valid patents. Haber Tr. 2438-39; RX 1013C.

FF CA 146. Abic tried numerous bases in the methylene chloride-water-TEBA system, including, in chronological order, potassium hydroxide, sodium hydroxide, potassium carbonate, sodium bicarbonate, calcium carbonate, magnesium hydroxide, ammonium hydroxide, triethylamine, and alumina, but in every case Abic obtained either low yields of N-alkylated product or high yields of

the unwanted dimer formation. Haber Tr. 2439-40; RPX-1145.

FF CA 147. [C] Haber Tr. 2440, 2443-43; RX 1145, RX 1024C.

FF CA 148. [C] Haber Tr. 2443-44; RX 1024C.

FF CA 149. [C] Haber Tr. 2445-46; RX 1024C.

FF CA 150. [C] Haber Tr. 2447-48; RX 1024C.

FF CA 151. [C] Haber Tr. 2449; RX 1024C.

FF CA 152. Abic's process is not a copy of the Tanabe process. Haber Tr. 2452.

FF CA 153. Abic's effort to develop its own process was wholly independent, and was not stimulated by knowledge of the '035 patent or of any counterpart. Haber Tr. 2452.

FF CA 154. Abic obtained patents on its process in the United States of America, Israel, Japan, Canada and Europe. Haber Tr. 2450.

FF CA 155. In the United States, Abic's patent application was examined by Examiner Bond, who cited the '257 patent and the '035 patent as prior art, and concluded that Abic's process was patentable over those references. Haber Tr. 2450; RX 1195 [CX 632].

FF CA 156. Professor Taylor is an organic chemist specializing in organic synthesis, synthetic methodology, and heterocyclic chemistry with emphasis on the development of new synthetic methods in heterocyclic and medicinal chemistry. Taylor Tr. 2586-87.

FF CA 157. Professor Taylor has been a professor of organic chemistry at Princeton for 41 years. He is currently the A. Barton Hepburn Professor of Organic Chemistry at Princeton. Taylor Tr. 2586.

FF CA 158. Professor Taylor has published over 400 articles, written three books in the field of heterocyclic chemistry, and is editor of a 60-volume series called *Chemistry of Heterocyclic Compounds* that is generally recognized as the reference series in heterocyclic compounds. He has obtained about 40 patents, and is a past Chairman of the Organic Division of the American Chemical Society. Taylor Tr. 2587-89.

FF CA 159. Professor Taylor is a consultant to chemical companies in the area of process development. Taylor Tr. 2592.

FF CA 160. Professor Taylor was awarded the American Chemical Society Award for Creative Work in Synthetic Organic Chemistry, the Gowland Hopkins Medal, the Fifth International Award in Heterocyclic Chemistry, and recently the C.Cope Scholar Award for his work in heterocyclic chemistry. Taylor Tr. 2592.

FF CA 161. Professor Taylor was accepted as an expert in the field of organic chemistry, including the subfields of organic chemistry and heterocyclic chemistry, including the seven-membered ring of heterocyclic amide compounds. Taylor Tr. 2593-94.

FF CA 162. Professor Mark S. Wrighton is an expert in surface chemistry and in the interpretation of differential scanning calorimetry curves. Wrighton Tr. 1607; RX 1679.

FF CA 163. Professor Wrighton is Provost and Professor of Chemistry at the Massachusetts Institute of Technology. He has been on the MIT faculty since 1972, and has been a full professor since 1977. Wrighton Tr. 1605.

FF CA 164. Professor Wrighton's general area of research involves surface chemistry, photochemistry and electric chemistry. Virtually all of his current research concerns the property of surfaces. Wrighton Tr. 1605-06.

FF CA 165. Professor Wrighton has published more than 400 scientific papers. Wrighton Tr. 1605.

FF CA 166. Professor Wrighton has published papers which contain the results of differential scanning calorimetry analyses. Wrighton Tr. 1606-07.

FF CA 167. Professor Wrighton was accepted as an expert in surface chemistry and in the interpretation of DSC curves. Wrighton Tr. 1607.

3. The Experts

Professor Liotta

FF CA 168. Dr. Liotta submitted a declaration in this investigation, which admittedly had some inaccuracies. The declaration also confused the claims of the patent with the examples cited in the specification. Liotta Tr. 1710-17. In an effort to show that the yield of Abic's process is not affected by the use of TEBA, the phase transfer catalyst, he reported incorrect yields (*id.* at 1713-15). Although Dr. Liotta declared that he had reviewed the prior art relating to the claims, he had only examined the prior art of phase transfer catalysis. *Id.* at Tr. 1712-13.

FF CA 169. Dr. Liotta referred to his postulated "surface solvent phase" as a "biphasic solvent system" only for purposes of this litigation; he had never referred to it before in those terms, and did it only to draw a comparison between Abic's solvent system and examples in the '035 patent. Liotta Tr. 1705-06.

FF CA 170. Dr. Liotta first concluded that the KOH-DMSO process was not equivalent to the '035 processes; then concluded that the KOH-DMSO process was equivalent; and then changed his mind again and said that they were not equivalent. Liotta Tr. 1708-09.

FF CA 171. Dr. Liotta obtained a patent on his theory of the "omega phase," a "surface solvent phase" which contained a phase transfer catalyst. *Id.* at 1750. In his patent he distinguished such omega phase systems as patentably distinct from conventional phase transfer catalyst processes. *Id.* at 1750-52. He admitted at his deposition that the Abic process is an example of such a conventional phase transfer catalyst process. *Id.* at 1753. But he also alleged that his theory of the omega phase was wrong, and that his patent was wrong. *Id.* at 1755.

FF CA 172. Dr. Liotta could not bring himself to admit that TEBA is a phase transfer catalyst, and kept calling it a "quat" and a "surfactant". Not only did Dr. Taylor testify that it is a phase transfer catalyst but Dr. Baldwin, an expert for complainant, referred to it as a phase transfer catalyst, as did Dr. Kende. CX 635; Liotta Tr. 1703-04; Kende Tr. 1340.

FF CA 173. Eventually Dr. Liotta admitted that TEBA is one of the most commonly used phase transfer catalysts (Liotta Tr. 1702), because he had written that in

his book. RX 3969; Taylor Tr. 2654; RX 3969; Liotta Tr. 1676, 1701; Taylor Tr. 2653.

FF CA 174. Dr. Liotta was forced to admit that there is no experimental data supporting his surfactant theory (Liotta Tr. 1676). He further admitted that he had not done any experiments of his own to show that TEBA is not acting as a phase transfer catalyst in the Abic system, and refused to accept Abic's data which shows increased yield when TEBA is used. Liotta Tr. 1835-37.

FF CA 175. For the above reasons, the Administrative Law Judge declines to accept the opinions of Dr. Liotta in support of complainants' positions.

Professor Atwood

FF CA 176. Dr. Atwood is primarily a single-crystal x-ray crystallographer. Atwood Tr. 3311.

FF CA 177. None of Dr. Atwood's publications is about x-ray powder diffraction. Atwood Tr. 3315, 3260.

FF CA 178. Unlike Dr. Jenkins, he hasn't written text-books about x-ray powder diffraction. Atwood Tr. 3260.

FF CA 179. Unlike Dr. Jenkins, Dr. Atwood does not belong to any organization devoted to x-ray powder diffraction. Atwood Tr. 3311.

FF CA 180. Unlike Dr. Jenkins, Dr. Atwood does not have any patents on x-ray powder diffraction equipment. Atwood Tr. 3317-18, 3260.

FF CA 181. Unlike Dr. Jenkins, Dr. Atwood does not design his own x-ray powder diffraction equipment. Atwood Tr. 3322-3323.

FF CA 182. Because the materials which are of interest in this investigation are powders, x-ray powder diffraction is the more pertinent expertise. Atwood Tr. 3313-14.

Dr. Jenkins' Qualifications

FF CA 183. Dr. Jenkins is currently employed as the principle scientist at the International Center for X-Ray Product Direction Data, a not-for-profit data base organization that archives and supplies about 65,000 powdered refraction patterns. Jenkins Tr. 2936-2937.

FF CA 184. Dr. Jenkins has been involved in X-ray powder refraction for about 35 years. Jenkins Tr. 2937.

FF CA 185. Dr. Jenkins worked for ESSO Research, Limited for 10 years, the last years spent in X-ray powder refraction analysis. He then worked at North American Phillips, where he was involved with the development of instrumentation and software for X-ray powder refraction. He also was involved in the application of the technique and teaching of the method of powder refraction. Jenkins Tr. 2937-2938.

FF CA 186. Dr. Jenkins obtained 6 patents for developmental work at North American Phillips, of which three were on equipment for X-ray powder refraction. Jenkins Tr. 2938

FF CA 187. Dr. Jenkins has published about 80 papers on X-ray powder refraction, and written three

books targeted at an audience of material scientists (geologists, mineralogists, chemists). The first book was written in 1972, and sold about 8,000 copies. The second was an audio course done in connection with the American Chemical Society. The third is coming out in March. Jenkins Tr. 2939

FF CA 188. Dr. Jenkins was accepted as an expert in X-ray powder refraction. Jenkins Tr. 2940.

4. TEBA/Phase Transfer Catalysis

FF CA 189. Dr. Liotta does not have any experimental evidence to support his opinion that TEBA in Abic's process acts as a surfactant. Liotta Tr. 1676.

FF CA 190. There is no documentary evidence of record in this investigation that TEBA acts as a surfactant or is regarded as a surfactant by people of ordinary skill in the art. Liotta Tr. 1701.

FF CA 191. TEBA is one of the most commonly used phase transfer catalysts in chemistry. Liotta Tr. 1701.

FF CA 192. Dr. Baldwin regards TEBA in Abic's system as a phase transfer catalyst. Liotta Tr. 1704-03.

FF CA 193. When TEBA is used in Abic's system, no dimer is formed, whereas when TEBA is not used, dimer is formed. Liotta Tr. 1801-03.

FF CA 194. In example 3 of the '035 patent, if methylene chloride is substituted for ethyl acetate, and no TEBA is present, no dimer forms, whereas, if TEBA is present, dimer forms. Liotta Tr. 1803-04.

FF CA 195. Solid-liquid phase transfer catalysis is different than liquid-liquid phase transfer catalysis. Liotta Tr. 1838.

C. The Fermion Process

FF CF 1. In February 1983, Dr. Lindholm (a Fermion development manager) assigned the project of developing a process for manufacturing diltiazem to Mr. Hytönen (who was then a product development chemist). Hytönen Tr. 2992-2993; Lindholm Tr. 3067.

FF CF 2. Dr. Lindholm testified at the hearing in part as an expert witness. Dr. Lindholm was accepted as an expert in chemical process design. Lindholm Tr. 3068-3069.

FF CF 3. Fermion's process development effort involved more than the single N-alkylation step. The Fermion diltiazem synthesis procedure today includes nine processing steps. The development effort commenced with the early steps in synthesis. Hytönen Tr. 2994.

FF CF 4. In early September 1983, Mr. Hytönen began working on the N-alkylation step of the diltiazem process. RPX 2022C, RX 2114C and RX 2115C, identified at Hytönen Tr. 2994-2995.

FF CF 5. The first N-alkylation experiment conducted by Mr. Hytönen was using '257 conditions so that he could obtain some N-alkylated TZP and learn how the '257 process worked. Hytönen Tr. 2994-2995.

FF CF 6. Mr. Hytönen conducted many tests with various base/solvent combinations for about one year. In September and October 1984, Fermion experimented with 2-butanone or methy ethyl ketone (MEK), [C] in September and October 1984. Hytönen Tr. 2995-3004; RX 2114C and RX 2115C.

FF CF 7. Mr. Hytönen read the '035 patent to exclude the use of MEK as a solvent. He testified as follows:

> Q When you reviewed the '035 patent, was there anything which suggested the use of MEK?
>
> A No, there was not.
>
> Q Why not?
>
> A They had only mentioned acetone, and they had – not even ketone mentioned. On the other hand, they had determined that the lower alkaline acetate, in the same way they could have determined – described also the lower ketones, if they had known that the reaction can be done with other ketones than acetone.
>
> Q Is MEK a homolog of acetone?
>
> A Yes.
>
> Q Do I understand that despite the facts that MEK is a homolog of acetone, the '035 patent still do not suggest the use of MEK to you?
>
> * * *
>
> THE WITNESS: It did not suggest any other ketone than acetone.

BY MR. KELLEY:

Q Why not?

* * *

THE WITNESS: I understand that Tanabe's researchers thought that other ketones cannot be used in this reaction.

Hytönen Tr. 3014-3015.

FF CF 8. Butanone is a homolog of acetone, *i.e.*, butanone has an additional methylene group.[1] It is not a lower alkyl acetate. Because of the additional methylene group, butanone has different properties from acetone. At the least, it can be said that butanone is more solvable in hydrocarbons than acetone; it is less solvable in water than acetone, it has a higher boiling point than acetone; it is less polar than acetone. Gokel Tr. 635, 637.

FF CF 9. Normally, if one of ordinary skill in the art wanted to seek how far one could extend the N-alkylation of '035 patent, one would try another ketone besides acetone, possibly 2-butanone (or MEK). By the same token, one of ordinary skill in the art familiar with a range of ketones would read the '035 patent, notice the specificity and exclusivity of the claim to the use of acetone, and conclude that other ketones were not

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[1] A homolog(ue) is defined as:

Member of a series of compounds whose structure differs regularly by some radical, e.g., $=CH_2$, from that of its adjacent neighbors in the series.

R. Grant & C. Grant, eds. *Grants & Hackh's Chemical Dictionary* 287 (1987).

included because they did not work. Taylor Tr. 2620-2621, 2784-85.

FF CF 10. While at university, Mr. Hytönen tried alternatives to acetone in an alkylation with potassium carbonate. One of the substitutions he tried was MEK for the acetone. He later had better success with another chemical. Although he tried these substitutions, Mr. Hytönen believes that many researchers (including his professor) think that certain alkylation reactions are specific to acetone. Hytönen Tr. 3015-3016, 3045-3046.

FF CF 11. Mr. Hytönen had experience with MEK at Fermion before starting his diltiazem development work. Hytönen Tr. 3016.

FF CF 12. Fermion conducts pilot tests on a scale that is smaller than industrial scale yet larger than laboratory scale, using instruments similar to those used for commercial manufacturing. Hytönen Tr. 3005.

FF CF 13. In October 1984, Fermion conducted a pilot plant test on the N-alkylation process using potassium carbonate/MEK as the base/solvent combination. This pilot plant test was a failure. RPX 2022C; Hytönen Tr. 3004-3005.

FF CF 14. After the October pilot plant failure with MEK, Fermion conducted additional experiments with a mixture of [C] as the solvent and [C] as the base; [C] and either [C], with and without [C]; [C] and either [C]; [C] with either [C]; [C] with [C]; [C] with [C]; and [C] with [C]. RX 2114C and RX 2115C (experiments B2449, B2454, B3367(a) and (b), B3371(a) and (b), B3372(a) and (b), B1048, B1049 and B3370).

FF CF 15. In 1985 Fermion conducted additional testing with the combination of [C] as the base/solvent combination for the N-alkylation step. RX 2114C and RX 2115C (experiments B1054, B3275(a) and (b), B1058(a) and (b), B3376(a), (b), (c) and (d), B1061, B1062(a), (b) and (c), B1064 and B1065(a), (b), (c) and (d)).

FF CF 16. Mr. Hytönen conducted further experiments in 1985 with the MEK and potassium carbonate process to determine why it had failed in the pilot plant. Hytönen Tr. 3007.

FF CF 17. Fermion also developed an alternative process using potassium carbonate/ethyl acetate, and produced diltiazem for commercial use. Hytönen Tr. 3005-3007.

FF CF 18. Fermion found the potassium carbonate/ethyl acetate combination to be unreliable on a commercial scale because potassium carbonate had to be added twice and one had to follow the reaction to completion, and to add DMC·HCl in different amounts based upon an analysis of the reaction. These procedures required the presence of a skilled chemist. Hytönen Tr. 3006-3007, 3047-3048.

FF CF 19. The operators of Fermion's process are not chemists, or laboratory technicians. They are individuals without formal chemical education. The skill of the operators is taken into account when developing a commercial process. Lindholm Tr. 3089-3090.

FF CF 20. The Finnish counterpart of the '035 patent was not in effect during the time period that Fermion

used the potassium carbonate/ethyl acetate combination. Hytönen Tr. 3007, 3047-48.

FF CF 21. In late 1985, Mr. Hytönen thought he had solved the problem with the MEK and potassium carbonate system, and conducted a second pilot plant test. Hytönen Tr. 3007.

FF CF 22. The second MEK and potassium carbonate pilot plant test was also a failure. Hytönen Tr. 3007.

FF CF 23. Fermion conducted further experiments with the MEK and potassium carbonate process, and conducted a third pilot plant test in January 1986 which was a success. Hytönen Tr. 3008.

FF CF 24. In the accused Fermion process, the N-alkylation step uses TZP, DMC·HCl, K_2CO_3, butanone (or "MEK") and water. Gokel Tr. 624; CX 192C.

FF CF 25. Fermion learned that the amount of [C] present in the MEK and potassium carbonate process was critical. Mr. Hytönen testified to this point as follows:

Q Did you determine what the cause of the problem was with your MEK process?

A Yes, we found out.

Q What did you determine caused the failure on the first pilot run?

A In the first pilot experiment, we had too much [C] in the reaction mixture.

Q Did you determine what the problem was in the second experiment?

A Yes. It had too little [C].

Hytönen Tr. 3008.

FF CF 26. The '035 patent contains no teachings that the amount of [C] in the process is critical. For example, complainants' expert testified as follows:

Q Nowhere in the '035 patent is there any explicit teaching that [C] is critical to the success of the reaction, is there?

A I think that's a fair statement.

Kende Tr. 1428.

FF CF 27. The '035 patent provided no guidance to Fermion and Mr. Hytönen in solving the problems encountered with the MEK and potassium carbonate process. In this regard, Mr. Hytönen testified as follows:

Q You testified a few minutes ago that the '035 patent did not provide any help in developing the present Fermion process. Do you recall that?

A That is true.

Q Why didn't it provide you with any help?

A For instance, there was no mention about – they did not mention the critical nature of [C]. On the contrary, they had examples in which there were reactions that had no [C] in them.

Q Did the '035 patent provide you with any help in determining the cause of the failures in the first two pilot plant runs with MEK?

A No, it did not.

Hytönen Tr. 3013-3014.

FF CF 28. Fermion learned that the MEK and potassium carbonate process did not work with either too much or too little added [C]. Hytönen Tr. 3008.

FF CF 29. After Fermion's success with the MEK and potassium carbonate N-alkylation process in the pilot plant, Mr. Hytönen began to experiment with making the process less sensitive to the amount of [C] present, and therefore "more reliable." Hytönen Tr. 3009-3010.

FF CF 30. Mr. Hytönen discovered that by reducing the ratio of [C], it was possible to reduce the sensitivity of the MEK and potassium carbonate to the amount of [C] present. Hytönen Tr. 3010.

FF CF 31. The present Fermion process has [C] added to the MEK. Hytönen Tr. 3008-3009, Lindholm Tr. 3090.

FF CF 32. Fermion discovered that its present process is extremely reliable, always proceeding to completion, i.e., all the TZP is consumed. Hytönen Tr. 3011; Lindholm Tr. 3075.

FF CF 33. The '035 patent does not provide any teaching that the [C] [C] will have any effect on the reaction. Mr. Hytönen testified as follows:

Q During the time that you were improving the MEK process, did the '035 patent provide any help?

A No, it did not.

Q Does the '035 patent teach a chemist what the effect of varying the relative amount of [C] will have on the process?

JUDGE HARRIS:You better ask that again.

BY MR. KELLY:

Q Let me break it into pieces and try to ask that again. Is there any description or teaching in the '035 patent that you will get a more reliable process by reducing the [C] [C]?

A No.

Tr. 3011-3012.

FF CF 34. The '035 patent provided no guidance to Fermion in reducing the ratio of [C] . Tr. 3011.

FF CF 35. Fermion's experts, Dr. Lindholm and Professor Magnus, testified that Fermion's process works in a different way than the process of the '035 patent claims. Lindholm Tr. 3075, Magnus Tr. 3178.

FF CF 36. Fermion conducted over [C] N-alkylation experiments between October 1983 and early 1986 in developing its process. Lindholm Tr. 3101; RX 2114C.

FF CF 37. In 1981, Tanabe attempted to use MEK as the solvent in the N-alkylation of TZP. RX 2047C, RX 2046C, RX 2094C and RX 3494C.

FF CF 38. In 1981, Tanabe tested and rejected MEK as the solvent for the N-alkylation of TZP. RX 2047C, RX 2046C, RX 2094C, RX 3494C.

FF CF 39. In 1981, Tanabe's experiments with MEK either resulted in no product or impure product. RX 2047C, RX 2046C, RX 2094C and RX 3494C.

FF CF 40. Fermion introduced evidence that a process which produced impure product would be considered a failure. *See* Hytönen Tr. 2999.

FF CF 41. The adverse consequence of too little or too much [C] in the '035 patent's potassium carbonate/ethyl acetate process was experienced by Tanabe in its commercial process, and is demonstrated by Tanabe's later 1991 testing. RX 2237C; Nakao Tr. 384, 420.

FF CF 42. Complainants' expert, Professor Gokel, testified that the way in which the process of the '035 patent claims worked was through a so-called "surface solvent phase" or a boundary phase. Gokel Tr. 941-942, 982.

FF CF 43. Complainants offered no evidence that a surface solvent phase was present in the Fermion process. The only tests offered by complainants were not N-alkylations and lacked both the TZP and DMC.HC1. CX 636, CX 680C and CX 681C.

FF CF 44. Dr. Lindholm testified as follows:

Q Have you reviewed any experiments which were conducted by Professor Gokel and Liotta in connection with this litigation?

A Yes, I have.

Q In Your opinion are those experiments relevant in any way to the matters involved in this litigation?

A They are not in my opinion.

Q Why not?

A In these experiments there were no starting material, no reagent that's the TZP or DMC. So in my opinion these experiments does not show anything about what happens when you do the real reaction.

Q Do you recall the testimony by Dr. Gokel that in his experiments he saw or observed a clump of potassium carbonate forming in the experiments with MEK?

A Yes, I remember.

Q Based upon your experience in the Fermion process, does the potassium carbonate form a hard clump upon the addition of water?

A No, it does not. We have not seen the thing occur either in laboratory or on the industrial scale.

Dr. Lindholm Tr. 3095-3096.

FF CF 45. In all of its experiments and commercial experience, Fermion has never observed the results obtained by complainants in complainants' tests in which neither TZP nor DMC.HC1 were present. Lindholm Tr. 3095-3096.

FF CF 46. Fermion's expert, Dr. Lindholm, testified that complainants' testing provides no basis for concluding that the Fermion process works in the same way as the process of the '035 patent. Lindholm Tr. 3095-3096.

FF CF 47. Fermion duplicated examples found in the '035 patent, and compared the results obtained with the

'035 patent solvents to those obtained when MEK was used as the solvent. CX 394

FF CF 48. Dr. Lindholm, one of Fermion's experts, concluded that based on these experiments, MEK was not equivalent to the '035 patent claim solvents in the N-alkylation of TZP. Dr. Lindholm testified as follows:

Q What is it about CX 394 that further supports your opinion?

A This CX 394 is a test series we run in the laboratory using the '035 patent examples, just as they are described in the patent. And for comparison, these examples, we substituted the solvent mentioned in the examples with MEK. And if we look at page 3, we see here a comparison of patent example 2 using either acetone or MEK.

From these experiments, we see that these two reactions run rather similarly. The butanone is a little bit faster than acetone. If we then go two pages forward and look at patent Example 4, this is now a dry system. We can see here that the acetone process works. After nine hours, there is really nearly no starting material left in the reaction.

But on the other hand, we can see that using MEK, we have virtually no reaction.

Taking these two examples together, as we should do, if these two solvents were equivalent, we would get the same results. We would even have a slightly faster reaction in MEK, as the boiling point is higher.

But as we do not have that, this means that these solvents can't be equivalent. If we turn one page back, we have patent Example 3.

> This is with ethyl acetate. From the numbers here, we can see that the reaction grows nicely in ethyl acetate.
> But on the other hand, we can see that using MEK, the reaction proceeds, but to a very small extent. After six hours reaction time, we have still roughly about 60 percent of the starting material left.
> This indicates that or at least shows that MEK and ethyl acetate are not equivalent.
>
> Q When you said the reaction went rather nicely in ethyl acetate, what did you mean?
>
> A I mean that the consumption of starting material was nearly complete.

Lindholm Tr. 3077-3078.

FF CF 49. Dr. Lindholm testified, that with the exception of '035 patent example 2, in all cases the substitution of MEK for the solvent of the patent example provided substantially different results. Lindholm Tr. 3077-3078.

FF CF 50. In patent example 3, the use of ground potassium carbonate in combination with ethyl acetate resulted in an N-alkylation reaction which proceeded to completion as described in the patent, i.e., within six hours. In contrast, with MEK and ground potassium carbonate, after six hours roughly 60% of the starting TZP remained. Lindholm Tr. 3077-3078, Hytönen Tr. 3138-3139.

FF CF 51. In patent example 4, Fermion was able to duplicate the results reported for acetone and powdery potassium carbonate, essentially complete TZP conversion within nine hours. However, when MEK was substituted for the acetone, the reaction did not proceed at all,

essentially all TZP remained unreacted. Hytönen Tr. 3077-3078.

FF CF 52. Patent example 5 did not proceed as written. CX 394.

FF CF 53. In patent example 6, the substitution of MEK for the methyl acetate of the example resulted in an N-alkylation which proceeded to completion in two hours, while with methyl acetate the reaction took thirty hours. CX 394.

FF CF 54. Fermion chose to use patent example 3 as exemplary of the '035 patent claim process because this was the sole '035 patent example repeated by complainants' expert, Professor Baldwin. Lindholm Tr. 3086.

FF CF 55. Subsequently, Fermion learned that patent example [C] closely resembles [C] process. Lindholm Tr. 3087.

FF CF 56. Complainants had testing conducted by Professors Baldwin, Gokel and Liotta. CX 635, CX 636 CX 680C and CX 681C.

FF CF 57 Professor Baldwin testified that he could not have predicted the results he obtained with MEK, 2-butanone:

Q Is there any way before this experiment you could have predicted this result?

A What result?

> Q That increasing [C] [with 2-butanone] would increase yield.
>
> A In the particular butanone system, no, I couldn't have predicted that.

RX 2238C.

FF CF 58. The only tests offered by complainants concerning the so-called "surface solvent phase" were not N-alkylations and lacked both the TZP and DMC.HC1. CX 636, CX 680C and CX 681C; Lindholm Tr. 3095-3096.

FF CF 59. Professor Baldwin's tests demonstrate that the mere substitution of MEK for the '035 patent's solvents did not result in an N-alkylation process which achieved yields and/or productivity comparable to that achieved by the Fermion commercial process. RPX 2004C-A. Lindholm Tr. 3092-3093.

IV. INVALIDITY – CLAIM 1 OF THE '035 PATENT IS INVALID UNDER 35 U.S.C. § 103

A. Background

FF D 1. During the United States prosecution of the '035 patent, Tanabe submitted to the PTO a Statement of Art in which Tanabe described its alleged invention as involving only certain specified base/solvent combinations, specifically stating that the "Applicants' invention" was N-alkylation:

> "[In] the presence of potassium hydroxide in acetone or potassium carbonate in acetone,

lower alkyl acetate, water-acetone, or water-lower alkyl acetate."

CX 2, paper 4 at 2-3.

FF D 2. In the Statement of Art Tanabe distinguished its alleged invention over the prior art by arguing that the invention produced yields of no less than 87% as opposed to 65-70% obtained with prior art processes.[2] XC 2, paper 4 at 2-3.

FF D 3. On December 21, 1981, Tanabe filed an application in Europe corresponding to the '035 patent application. RX 3325. On June 1, 1984, Tanabe's EPO application was rejected over the '967 and '257 patents. RX 3325.

FF D 4. The '967 patent taught the use of "alkali metal hydroxides" in a variety of solvents including toluene to attach DMC to a benzothiazepinone differing from TZP by only a single R group at the three position of the seven-membered ring. Potassium hydroxide and sodium hydroxide are examples of alkali metal hydroxides. RX 1103; Gokel, Tr. 870-82, 877-78, 881; Taber, Tr. 2159-60. In response to that rejection, on October 1, 1984, Tanabe submitted a twelve page document urging that the application be approved over the '257 and '967 patents. Included in this response were five pages of attorney argument and what Tanabe referred to as a "Comparative Test Report" which, Tanabe claimed, demonstrated the patentability of its claimed process over

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[2] Tanabe did not disclose Krapcho's U.S. Patent 3,075,967 (the " '967 patent") to the U.S. Patent and Trademark Office ("PTO") during the original prosecution of the '035 patent. CX 2.

prior art disclosures that used, *inter alia*, sodium carbonate and toluene. RX 3929C. Specifically, Tanabe represented that the Comparative Test Report

> "[S]hows that the *specific combination of bases and solvents, i.e.*, potassium hydroxide in acetone or potassium carbonate a solvent selected from acetone, lower alkyl acetate, a mixture of acetone and water and a mixture of lower alkyl acetate and water, leads to surprising results of the method according to the invention."

RX 3929C at 705 (emphasis added).

FF D 5. Tanabe's submission analyzed the experimental data reflected in the Comparative Test Report and explained as follows to the EPO:

> For example, when the condensation reaction was carried out by the use of sodium hydroxide or sodium carbonate as the base, the yield of the product was less than 10% even if acetone was used as the solvent. Moreover, when sodium amide or sodium hydride was used as the base, the yield of the product was not more than 12.4% in the case where toluene or dioxane was used as the solvent. Furthermore, even if potassium hydroxide or potassium carbonate was used as the base, the yield of the product was less than 30% in the case where dioxane, toluene or methanol was used. (RX 3929C at 706.)

Tanabe further explained that:

> [j]udging from the facts (i) that the references cited by the Examining Division teach neither the use of potassium carbonate as the base nor the use of the *specific* base-solvent combinations to be employed in the method of the present invention; (ii) that,

> when the condensation reaction was carried out by the use of sodium hydroxide or sodium carbonate as the base, the yield of the product was less than 10%; and (iii) that, even if potassium hydroxide or potassium carbonate was used as the base, the yield of the product was less than 30% in the case where dioxane, toluene or methanol was used, it is obvious that the above-mentioned advantageous features of the present invention have never been taught nor suggested in the references cited by the Examining Division. Thus, the replacement of sodium hydride and dimethylsulfoxide *by the specific base-solvent combinations* of the present invention is unobvious over the cited references. Due to the superior and surprising results *obtained by the method of the invention*, the present application possesses level of inventiveness necessary for its patentability.

RX 3929C (emphasis added).

FF D 6. Tanabe made identical arguments to numerous other patent offices, including those of Israel and Finland. 3338C; 3233C.

FF D 7. Reexamination of the '035 patent was requested by Respondent Abic, and supported by a declaration of Dr. Taylor. RX 1085 (See RX 2193).

FF D 8. The examiner initially agreed with Dr. Taylor, and rejected all the claims of the '035 patent. RX 1603 (RX 2193, RX 2204).

The bases for the rejection included:

(a) The '257 patent showed a conventional method of N-alkylation;

(b) Pachter and subsequent references showed the "widely used" N-alkylation of N-aryl amides with the same bases (potassium hydroxide, potassium carbonate) and the same solvent (acetone) as the '035 patent;

(c) British '119 and Nagarajan showed dimethylaminoethylation (i.e., reaction with DMC) of dibenzoxazepinones;

(d) Johnstone "further illustrat[ed] the value of the Pachter et al. technique."

RX 1603.

FF D 9. In response, Tanabe submitted declarations by Drs. Baldwin and Kende which argued that:

(a) The Pachter technique was not widely known;

(b) Pachter did not render the '035 patent obvious because it (i) disclosed only amides which were not cyclic and (ii) did not disclose DMC as an alkylating agent;

(c) British '119 and Nagarajan were limited to "nitro-substituted" amides, and thus not relevant to N-alkylation of TZP which had no nitro substituent;

(d) Johnstone was not pertinent;

(e) A number of potential side reactions, including retro-Michael reaction, ring-cleavage, O-alkylation, and carbonyl O-alkylation might occur, and might prevent high yields of the '035 patent.

RX 1658, RX 1329.

FF D 10. During the reexamination of the '035 patent, the examiner was presented with about 172 prior art references. RX 1603.

FF D 11. The examiner accepted some of Tanabe's arguments, and in deciding to issue a reexamination certificate, held that the prior art then of record did not establish the obviousness of the '035 patent. RX 1653; RX 1654; Taylor Tr. 2714-15, 2924-26; RPX 1149; RPX 1151.

FF D 12. The N-alkylation process described in the '035 patent is typical of the types of projects that process development chemists would have undertaken in 1981. Pachter Tr. 1495-96.

FF D 13. It is generally accepted that when potassium hydroxide is used to deprotonate an amide, including TZP, water is produced as a side product. Gokel Tr. 103940.

FF D 14. The patent examiner was not told that the prior art disclosed hydrous systems for the N-alkylation of benzothiazepinones. Further, the patent examiner said nothing during the interview which Dr. Baldwin attended to indicate he was aware of the prior art teaching the N-alkylation of benzothiazephine type compounds in hydrous conditions. RX 4038C; Kende Tr. 1431-32.

FF D 15. In his declaration submitted to the examiner during the Reexamination (RX 3132), Dr. Kende did not advise the examiner that in 1981, Yamawaki disclosed hydrous systems involving the use of potassium carbonate, sodium hydroxide and potassium hydroxide as bases which are excellent alternatives to the conventional bases used in N-alkylation methods. Kende Tr. 1355-57.

FF D 16. In granting the request for reexamination, the examiner stated in part as follows:

> The arguments concerning the possibility of side reactions by Taylor, Baldwin in [sic] Kende are not seen as having great weight in this particular case one way or another. Nor are the arguments concerning the use of DMC.HC1.

RX 1653.

FF D 17. The chemistry of organic compounds revolved around the chemistry of functional groups. Kende Tr. 526; Taylor Tr. 2780-81.

FF D 18. Functional groups are more important than ring structure in determining chemical reactivity. Taylor Tr. 2780.

FF D 19. The functional group known as an "N-aryl amide," which is part of the structure of TZP, has the following general structure:

[Diagram Omitted In Printing]

Kende Tr. 1457-58; RPX 4023.

FF D 20. One can choose reaction conditions by focusing on the functional group on which one wishes to carry out the chemical transformation. The ring framework to which the functional group is attached plays a minor role, if any, in the functional group chemistry. In organic chemistry, synthetic reactions depend upon and are focused on the properties of the functional group. Taylor Tr. 2780.

FF D 21. The inventors of the '035 patent knew prior to 1981 that the N-alkylation reaction worked and that

commercially feasible methods existed. The only question faced by the inventors was whether cheaper, easier to handle bases or solvents could be used. RX 3739-C; RX 3737-C.

FF D 22. The process claimed in the '035 patent involves the conversion of an N-aryl amide, *i.e.*, TZP or acetyl-TZP, to an N-alkylated amide. RPX 4023; RPX 4015; Kende Tr. 1457-1458; Pachter Tr. 1497.

FF D 23. In attempting to improve on the '257 patent, a person of ordinary skill in the art would have first looked for art related to benzothiazepines. Then, one would have looked for references to work in related systems, which in this case in N-aryl amides, because that is the reactive part of the TZP molecule for alkylation. The person of ordinary skill would have found references such as Pachter et al., "Methylation of Some Amides in Acetone," 74 J. Am. Chem. Soc. 1321-22 (1952) ("Pachter reference"); Worley et al., "2-Dialkylphosphonyl- and 2-Alkylidene-3, 4-dihydro-3-oxo-2H-1,4-benzothiazepines," 40 J. Org. Chem. 1731-34 (1975) ("Worley"); Clark et al., "Synthesis and Analgesic Activity of 1,3-Dihydro-3-(substituted phenyl) imidazo[4,5-b]pyridin-2-ones and 3-(substituted phenyl)-1,2,3-triazolo[4,5-b]pyridines," 21 J. Med Chem. 965-78 (1978) ("Clark"); Nagarajan et al., "Condensed Hetrerotricycles: Amino & Aminoalkyridibenz [b,f][I,4] oxazepin-II(IOH)-ones," 12 Indian J. Chem. 236-46 (1974) ("Nagarajan"); and Latif and Sattar, "A Note on the Alkylation of Amides," 32 J. Indian Chem 489-90 (1955) ("Latif"). Pachter Tr. 1496-97.

FF D 24. In connection with its efforts to synthesize the diltiazem molecule, Abic assembled as many references on benzothiazepines as it could. Significantly, Abic found the field of benzothiazepines relevant, and did not limit its research only to the N-alkylation of TZP. Abic also conducted a chemical structure search. A chemical structure search is a search based on a chemical nucleus, regardless of what structure is attached to it. For this search, Abic selected a six-member ring with a seven-member ring attached to it, the seven-member ring containing sulphur and nitrogen. This search would have included the Krapcho patents, but not the Pachter or Worley references because they do not have the ring structures associated with benzothiazepines. Haber Tr. 2453-59.

FF D 25. It is not clear from the record whether Abic personnel already had knowledge of the Pachter reference before the Abic literature search was conducted. No one at Abic, especially Dr. Haber, is the hypothetical person of ordinary skill in the art who is presumed to have knowledge of all prior art. *See* Haber Tr. 2453-59.

B. The Prior Art

1. The Kugita '257 Patent

FF D 26. Complainants' expert, Dr. Kende, distinguished the '035 patent over the '257 patent by stating:

> It teaches the use of milder bases than the '257 in that sense certainly it's mild conditions. Mild

> in this sense means a base which is not so strong that it will be irreversibly deprotonated.

Kende Tr. 1156.

FF D 27. During the Reexamination of the '035 patent, the Examiner issued an Office Action wherein he stated that "Kugita ['257] show the conventional process of production of benzothiazepinones such as diltiazem by alkylation. . . . " RX 1603 (¶4); Taylor Tr. 2706.

FF D 28. In determining to accept Abic's petition for reexamination the examiner concluded that:

> It would be obvious for one of ordinary skill in the art to use the Pachter et al technique in the Kugita et al. ['257] process. Since the desirability of Pachters' technique has been long established, it would be obvious to use it in a process such as that of Kugita et al. One would be motivated to do so in the desire that superior results would be achieved. The chances for success would be excellent.

RX 1603.

FF D 29. The '257 patent teaches the N-alkylation of the identical substrate of the '035 patent, TZP, using the alkyl halide DMC.HC1 to yield the identical alkylated product. RX 3652; Taber Tr. 2166; RX 4038C.

FF D 30. The '257 patent disclosed a process for the N-alkylation of the identical substrate as the '035 patent using as a base an alkali metal, alkali metal hydride, or alkali metal amide, and as a suitable solvent, for example, dioxane, toluene, xylene, or DMSO. RX 3652.

FF D 31. The N-alkylation reaction disclosed in the '257 patent probably proceeds through the aziridinium. Taber Tr. 2166; Gokel Tr. 850; RX 4038-C.

FF D 32. The '257 patent teaches that benzothiazepinones, which are N-aryl amides, could be alkylated under rigorous conditions. Pachter Tr. 1499.

FF D 33. In looking to improve upon the '257 process, a process development chemist would rapidly realize that the reactive portion of the TZP molecule is what is known as an "N-aryl amide". RPX 4023; Pachter Tr. 1496.

FF D 34. The '257 patent (the only patent cited in the '035 patent) teaches that benzothiazepinones, which are N-aryl amides, can be alkylated under rather rigorous conditions (*e.g.*, NaH/DMSO) using somewhat dangerous bases that can result in explosions, solvents that are inconvenient, and which result in low yields. Pachter Tr. 1499; RX 1229, 1460.

FF D 35. Given only the '257 patent and the Pachter reference, a person would have had an "excellent" chance (90 percent) of success, *i.e.*, producing some yield even with the possibility of side reactions. Pachter Tr. 1504, 1508-09, 1511-12; Taylor Tr. 2703.

2. The Pachter Reference

FF D 36. The Pachter reference was published in 1952 as a result of work done by Dr. Pachter towards his Ph.D. thesis under the tutelage of Dr. Kloetzel. Pachter Tr. 1499-51; RX 3770; RX 3769.

FF D 37. The N-aryl amide structure, which is a part of TZP, is also a part of each of the substrates alkylated by Dr. Pachter in 1952. Kende Tr. 1458; RPX 3770B; RPX 4023.

FF D 38. RPX 4023 depicts an N-aryl amide. Pachter Tr. 1497.

FF D 39. The Gabriel synthesis is the alkylation of an activated amide. It is not an N-aryl amide. Every first year organic chemistry student gets to learn what the Gabriel synthesis is. In studying the literature Pachter found that sometimes the Gabriel syntheses is carried out in acetone. RX 3769. The Pachter reference applied the known Gabriel synthesis conditions to N-aryl amides. It worked and he concluded that it appears to have general application to N-aryl amides. Pachter Tr. 1529-30, 1601-02.

FF D 40. Pachter's process used the same base-solvent combination as the '035 patent, namely, potassium hydroxide and acetone, in hydrous reaction conditions. Pachter Tr. 1502-03; Kende Tr. 1277 and 1286-1287.

FF D 41. The Pachter system is a hydrous system. Kende Tr. 1461.

FF D 42. Pachter disclosed the following N-alkylation of an N-aryl amide using KOH and acetone:

[Diagram Omitted In Printing]

R^1X above represents an alkyl halide. RPX 3770B; Pachter Tr. 1504-05; Kende Tr. 1456-57.

FF D 43. Pachter disclosed successful N-alkylation using methyl iodide as the alkyl halide, in which R was methyl ($-CH_3$) or phenyl [Diagram Omitted In Printing]. RPX 3770B; Pachter Tr. 1504-05.

FF D 44. Pachter's KOH/acetone reaction conditions are hydrous reaction conditions. Kende Tr. 1286-87.

FF D 45. It was important to have as much of the base in solution as possible in order for the reaction to take place rapidly. Therefore, Dr. Pachter chose potassium hydroxide as the base because potassium bases are more soluble in acetone than sodium bases. Pachter Tr. 1527-28.

FF D 46. Dr. Pachter chose acetone as the solvent since he knew he could get his compounds into the acetone solution quite readily and because it would provide a good medium for the reaction. Pachter Tr. 1528.

FF D 47. The Pachter reference discloses the N-alkylation of several N-aryl amides using the base/solvent combination KOH/acetone. Each of the N-alkylated amides has an aryl, or benzene ring, and a carbonyl. The benzene ring and the carbonyl flank the nitrogen, which is to be alkylated. Pachter Tr. 1504-05; CX 638A; RX 3770; RPX 3770B.

FF D 48. Pachter investigated the N-alkylation of N-aryl amides over a range of conditions, including those in which the amide was activated toward alkylation, deactivated, and neither activated nor deactivated, thus demonstrating the general applicability of his reaction procedure. Pachter 1504-07; Kende Tr. 1458-59; RX 3770; RPX 3770B.

FF D 49. Using the same KOH/acetone base-solvent combination claimed in the '035 patent, Pachter discovered and disclosed that alkylation can be accomplished "conveniently and in good yield." RX 3770.

FF D 50. In the five specific examples described by Pachter, the yields of N-alkylated amides were from 81% to 90%. RPX 3770B.

FF D 51. Although certain of the N-aryl amides alkylated by Dr. Pachter had potential alternative reaction sites, they did not interfere with the desired reaction of the amide. Pachter Tr. 1508, 1532-33; RPX 3770B.

FF D 52. Some of the compounds alkylated by Pachter were complex. Pachter Tr. 1568.

FF D 53. The (N-methylbenzamido) diphenylamine compounds that Pachter alkylated had two possible sites for alkylation, the amide nitrogen and the amine nitrogen. Alkylation of the amine did not interfere with alkylation of the amide. Pachter Tr. 1508.

FF D 54. Dr. Pachter decided to use potassium hydroxide as the base because he knew it was more soluble in organic solvents like acetone or ethyl acetate than the sodium base. Pachter Tr. 1527.

FF D 55. Dr. Pachter used potassium hydroxide and acetone based upon the teachings of the prior art that alkylation of an amide in what is known as the Gabriel synthesis succeeded with potassium hydroxide, but failed under '257 conditions. RX 3769 at 46-47; Pachter Tr. 1528-30.

FF D 56. In 1952, when Dr. Pachter applied the conditions of the Gabriel synthesis to his own N-alkylation reactions, he was a little less than someone skilled in the art because he had not yet received his Ph.D. degree. Taylor Tr. 2798.

FF D 57. The person of ordinary skill in the art would do exactly what Dr. Pachter did in 1952 – if you want to carry out a reaction on a substrate, you look at what's been done that's analogous and see if it can be applied to the system. The closer the analogy, the closer the example from the literature, perhaps the greater confidence one has. But there is a standard way of doing organic chemistry and this is the way people skilled in the art do it. Taylor Tr. 2798-99.

FF D 58. In 1952, Dr. Pachter concluded that the alkylation procedure with potassium hydroxide and acetone seems to have "general application." Pachter Tr. 1530.

FF D 59. Following the publication of the Pachter reference, the Pachter base-solvent combination of KOH/acetone for the N-alkylation of aryl amides became well-known and well-recognized by those of ordinary skill in the art as a generally applicable procedure for the N-alkylation of aryl amides. Taylor Tr. 2737, 2740.

FF D 60. In his declaration submitted to the Patent office during the Reexamination, Dr. Baldwin suggested that a paper by Yamawaki suggested that the Pachter method is not general. RX 1658; Taylor Tr. 2740-2741.

FF D 61. Yamawaki's experiments were not limited to N-aryl amides. Taylor Tr. 2740-2741.

FF D 62. Respondents presented over a dozen references in this investigation which describe Pachter-type N-alkylation of N-aryl amides. Taylor Tr. 2744-2745.

FF D 63. In explaining why the N-alkylation reaction occurs at one nitrogen rather than another in one of

the amides discussed in his reference, Dr. Pachter explained that under neutral conditions both nitrogens are extremely weak bases. However, under basic conditions, only the nitrogen of the N-aryl amide is sufficiently acidic to be deprotonated and form an anion. Pachter Tr. 1532.

FF D 64. Every attempt known to Dr. Pachter to N-alkylate an N-aryl amide using Pachter conditions has succeeded. Dr. Pachter knows of about 100 such N-alkylations. Pachter Tr. 1565, 1567.

FF D 65. The prior art showed that Pachter conditions worked for the N-alkylation of all N-aryl amides and some others. Taylor Tr. 2702.

FF D 66. In 1981, no reference was known of in which Pachter's conditions did not work for the alkylation of an N-aryl amide. Today, no reference is known of in which the use of Pachter's conditions not to work for the alkylation of an N-aryl amide. *See* Pachter Tr. 1565; Kende Tr. 1286.

FF D 67. Complainants' expert agreed with the remark made by the examiner that by 1981, the "desirability" of the Pachter KOH/acetone technique has long been established. Complainants' expert did not, of course, take the position that the "applicability" of the technique had been established. Kende Tr. 1280.

FF D 68. In Pachter's process, water is formed in the reprotonation step. Kende Tr. 1287.

FF D 69. The alkylation of an amide under Pachter conditions produces water as a side product. Gokel Tr. 1039-40; RPX 1096.

FF D 70. The Pachter reference teaches one of ordinary skill in the art that one can alkylate an amide under hydrous conditions. Kende Tr. 1286-87, 1461; CX 638A.

FF D 71. During the reexamination of the '035 patent, the examiner stated that "Pachter et al. show the widely used alkylation of aryl amides." RX 1603 (PTO Office Action); Taylor Tr. 2706-07.

FF D 72. Several references describe Pachter conditions in general terms, *e.g.*, Worley (RPX 1094), Johnstone (RX 1137), Latif and Sattar (RX 1605), Clark (RPX 1093). Kende Tr. 1290-99, 1306-08, 1380; Pachter Tr. 1509.

FF D 73. The process taught in the Pachter reference was an improvement over earlier processes because it achieved the N-alkylation reaction by switching the known bases and solvents (later disclosed in the '257 patent) to potassium hydroxide/acetone (those later described in the '035 patent). In his paper, Dr. Pachter showed that in relatively short reaction times under very convenient conditions, one could rapidly and in good yield produce the necessary compound. Indeed, Dr. Pachter's paper teaches that some compounds are inactive under '257 conditions, but easily alkylated under Pachter conditions. Kende Tr. 1284-85, 1460-61; Pachter Tr. 1502-04, 1524; CX 1, 638A; RX 3770; RPX 3770B.

FF D 74. The Pachter reference disclosed that the usual method for alkylating N-aryl amides until his publication included the use of dangerous metals, metallic sodium, or sodium hydride in inert solvents (*i.e.*, '257 conditions). Pachter Tr. 1501-02.

FF D 75. Pachter, in 1952, had taught that the substitution of KOH/acetone for the base-solvent combinations used in the '257 patent would avoid the dangers and inconveniences of such bases and solvents and could actually increase yields. RX 3770; Pachter Tr. 1501-03.

FF D 76. The specification of the '035 patent is similar to the first few paragraphs of the Pachter reference, *e.g.*, both describe previous methods as inconvenient, dangerous, and resulting in low yields. Indeed, Dr. Pachter initially thought the '035 patent drafters "copied paragraph 1" of his paper. Pachter Tr. 1503-04; CX 1; RX 3770.

FF D 77. Pachter recognized the problem which according to complainants, the '035 patent is said to have solved. Pachter disclosed in his 1952 article that, "[t]he usual method for the alkylation of amides, involving metallic sodium and an inert solvent is at best a rather inconvenient and somewhat dangerous procedure." Pachter then suggested replacing the sodium, *i.e.*, a '257 base, with the KOH/acetone system, the same substitution proposed by the '035 patent. RX 3770; CX 1; RX 3652; Pachter Tr. 1503-04; Kende Tr. 1284-85.

FF D 78. Using the same KOH/acetone base-solvent combination claimed in the '035 patent, Pachter disclosed that the N-alkylation can be "accomplished conveniently and in good yield" in a relatively short period of time. RX 3770.

FF D 79. Given the Pachter reference, all the prior art that discusses Pachter as a general procedure, and ignoring the possibility of side reactions, complainants' expert admitted that it would have been obvious that TZP can be alkylated with methyl iodide under Pachter

conditions to give at least a yield of 10% of desired product. Kende Tr. 1318-19.

3. Worley

FF D 80. Worley describes the successful N-alkylation of a N-aryl amide lactam under Pachter conditions using alkylating agents methyl iodide and ethyl bromo acetate, reporting a 73% yield. Kende Tr. 1290-92; Pachter Tr. 1510-11; RPX 1094.

FF D 81. Lactams, including TZP, are cyclic amides. Kende Tr. 1290.

FF D 82. Worley taught that Pachter conditions can be applied to a lactam (a cyclic amide) as well as to Pachter's cyclic amides. Kende Tr. 1291; Pachter Tr. 1510-11.

FF D 83. The compound alkylated by Worley had a sulfur atom which, like the sulfur atom of TZP, can transmit its effects through the aromatic ring down to the nitrogen. If the sulfur atom of TZP were to affect the N-alkylation reaction of Pachter, such a deleterious effect would have been seen in Worley. Worley obtained a good yield when using Pachter conditions. Pachter Tr. 1511.

FF D 84. Worley provided assurance that the sulfur atom in the TZP ring would not inhibit the N-alkylation reaction. Taylor Tr. 2703.

FF D 85. The amide group in Worley has approximately the same acidity as the amide group in TZP. Kende Tr. 1304.

FF D 86. Worley is a six-membered ring. In terms of ease of alkylation, a distinction between the six-membered ring of Worley and the seven-membered TZP ring is not necessary. On size alone, complainants' expert would not draw any distinction between six member rings and seven member rings. Kende Tr. 1310.

FF D 87. In 1975, Worley used KOH/acetone in the following N-alkylation reaction, stating that the procedure used was the "general procedure of Pachter and Kloetzel for the alkylation of [N-aryl] amides with potassium hydroxide in acetone" (the N-aryl amide structure shown in bold type):

[Diagram Omitted In Printing]

RX 3824; RPX 3824A; Kende Tr. 1291-93; Pachter Tr. 1509-10.

FF D 88. The Worley compound is a very good model for TZP. Both compounds are N-aryl amides; both compounds have heterocyclic ring systems; both compounds are aromatic and both compounds have sulfur in the same position. Taylor Tr. 2738-2739.

FF D 89. Worley teaches using the "general procedure of Pachter." Pachter Tr. 1509-10; RX 3824 at 1733.

FF D 90. Worley does not report any reaction (or side reaction) of the sulphur atom. Kende Tr. 1303; RPX 1094.

FF D 91. Dr. Taylor believes that Worley, which uses a substrate having a 6-membered heterocyclic ring, is closer prior art to the '035 patent than Nagarajan, which uses a substrate with a 7-membered heterocyclic ring (like TZP) but is an oxazepinone. Taylor Tr. 2708-10.

FF D 92. Given the '257 patent, the Pachter reference, as well as Worley, it would have been even more obvious that one could alkylate TZP under the general Pachter conditions – chances of success would have increased to 95% since the Worley compound is more similar to TZP in that it is a lactam and it also contains a sulfur atom. Pachter Tr. 1511-12; Taber Tr. 2181-82; Taylor Tr. 2703.

4. Johnstone

FF D 93. In 1969, a technical article, Johnstone et al., "A Rapid Method of N-alkylation of Amides," 16 J. Chem. Soc. 2223-24 (1969) ("Johnstone"), reported the use of Pachter conditions to alkylate a substrate that is not an N-aryl amide, calling Pachter "a singular example of easy alkylation of an amide. . . . " RX 3848; Kende Tr. 1294.

FF D 94. In Johnstone, a base/solvent combination of potassium hydroxide/acetone worked, whereas sodium carbonate/acetone did not work. Kende Tr. 1296-97; RX 1137.

FF D 95. The Johnstone use of the Pachter reference and the use of Pachter conditions is one further indication that people working on amides looked to reactions performed on other amides, even if they involved very different substrates. The Johnstone authors managed very successfully to use what they termed an "easy alkylation." Taylor Tr. 2710-11.

FF D 96. Johnstone shows an appreciation of the potential generality of the Pachter technique, and that the

Pachter technique was in fact used as a general technique. Taylor Tr. 2711.

5. Clark

FF D 97. In 1978, Clark et al. reported the following N-alkylation reaction, where the N-aryl amide "was alkylated with alkyl halide and refluxing acetone solution in the presence of powdered potassium hydroxide according to the method of Pachter and Kloetzel":

[Diagram Omitted In Printing]

RX 3841 (the N-aryl amide structure is in bold type); Kende Tr. 1306-07.

FF D 98. Clark discloses 40 examples of hydrous reactions on 40 compounds using Pachter conditions (a base/solvent combination of potassium hydroxide/acetone), and reports satisfactory yields. Kende Tr. 1306-08; Taylor Tr. 2772-73; RPX 1093.

FF D 99. The N-alkylation reaction reported in Clark is hydrous. Kende Tr. 1306.

FF D 100. Clark reports the use of Pachter conditions with dialkylaminoethyl chloride: a dialkylaminoethylating agent which, like DMC, reacts through the aziridinium ion. Kende Tr. 1308; Taylor Tr. 2772-73.

6. Latif

FF D 101. Latif refers to Pachter as a general process for the alkylation of amides that is applicable for almost all types of alkyl halides. RX 1605.

FF D 102. Latif observed some limitations for use of the Pachter technique, but not with respect to any N-aryl amide. RX 1605; Pachter 1573-74.

7. Nagarajan

FF D 103. In the May 31, 1994 Notice of Intent to Issue Reexamination Certificate, the examiner stated:

> Perhaps the most pertinent references are the British Patent and Nagarajan et al. Both of these references show the aminoalkylation of lactams which bears some structural relationship to those of Kugita et al. using a process similar to Pachter et al. However, all of the compounds which are amino alkylated contain an activating nitro group when the Pachter-type process is employed. Nagarajan et al. shows that where no activating nitro group is present that the more harsh methods, similar to those of Kugita et al., must be employed. This indicates that where, activating nitro group is not present, the Pachter et al. technique is not operable. This teaches away from the process of Gaino et al. the patent being reexamined here.

RX 1654.

FF D 104. Nagarajan used '257 conditions on the unsubstituted, *i.e.*, no nitro-substitution, compounds

because these were the conditions everyone was using. Pachter Tr. 1526.

FF D 105. Nagarajan does not explicitly state that the procedure using potassium carbonate and acetone is not suitable for non-nitro substituted compounds. Kende Tr. 1361. Dr. Kende submitted a declaration during the reexamination wherein he suggested that the procedure using potassium carbonate and acetone is not suitable for non-nitro substituted compounds of Nagarajan. Dr. Kende read this in by implication. This implication had the obvious effect of misleading the PTO examiner and is totally incorrect. RX 3132; Kende Tr. 1360-61.

FF D 106. Under '257 conditions, a nitro group is a deactivating group, Pachter Tr. 1588.

FF D 107. To state that the presence of the nitro group could make alkylation easier or harder would be speculation. Kende Tr. 1365.

FF D 108. Like Fones, (who came before Pachter) Nagarajan had found that he was unable to alkylate nitro-substituted compounds under '257 conditions, whereas he found the Pachter process worked fine. Pachter Tr. 1526-27.

FF D 109. Nagarajan started with '257 conditions and then switched to Pachter conditions. Pachter Tr. 1587-88. Nagarajan went to Pachter conditions because alkylation did not process under '257 conditions. Pachter Tr. 1542.

FF D 110. Dr. Kende, in his declaration submitted to the examiner during reexamination, on page 17 referenced Nagarajan's discussion of ring cleavage. The ring

cleavage discussed in Nagarajan would not occur with TZP. RX 3132; Kende Tr. 1367-68.

FF D 111. Dr. Baldwin, in his declaration submitted to the examiner during the reexamination, stated that "the Nagarajan reference suggested that ring cleavage was a distinct possibility under Pachter base/solvent conditions of seven membered oxazepines. (*See, Experimental,* page 245(d)). This too would have taught away from the process of the '035 patent." RX 1658. Dr. Kende stated that he did not see the connection between Nagarajan and the '035 substrate. RX 1658; Kende Tr. 1368.

FF D 112. There is no connection between ring opening reported in Nagarajan and alleged ring opening in TZP. Kende Tr. 1375; Taylor Tr. 2720.

FF D 113. As expressly stated in Nagarajan, the ring cleavage in Nagarajan depends upon the presence of the nitro group. There is no nitro group present in TZP. Taylor Tr. 2712, 2720-22.

FF D 114. In his declaration submitted to the PTO, Dr. Baldwin identifies ring cleavage as a consequence of the nitro group. RX 1658; Taylor Tr. 2719. Dr. Baldwin's declaration was misleading regarding Nagarajan, the teaching of ring cleavage, and the possibility that it would suggest ring cleavage in the '035 case where there is no nitro group. Taylor Tr. 2723.

FF D 115. Nagarajan did not report ring cleavage with potassium carbonate and acetone. Kende Tr. 1369.

FF D 116. Nagarajan reported ring cleavage with '257 conditions and no ring cleavage under Pachter conditions. Taylor Tr. 2725-27, 2729-31; Kende Tr. 1369. If

there is no nitro group, as there is none with TZP, there is no problem of ring cleavage, and also, under Pachter conditions there is no problem of ring cleavage. Kende Tr. 1369-70; Taylor Tr. 2720-22.

FF D 117. Contrary to the examiner's opinion, the Nagarajan paper does not teach that a hydrous system for N-alkylation will not work with compounds that are unsubstituted with the nitro substituent. Pachter Tr. 1523.

FF D 118. Page 245, Procedure D of Nagarajan shows that Nagarajan, like Fones, attempted to alkylate with DMC using '257-like conditions, heating for a long time (4 hours), resulting in 9% yield, 35% starting material and the remainder as decomposed material. RX 3820; RPX 3820A; Pachter Tr. 1524-25.

FF D 119. Nagarajan (RX 3820) methylated (N-alkylated) with methyl iodide. After succeeding with methyl iodide, Nagarajan used DMC. Pachter Tr. 1534.

8. Burton

FF D 120. The N-alkylation of aryl amides using the base-solvent combination K_2CO_3-acetone was taught as early as 1968 by Burton et al., "Halogeno-o-phenylenediamines and Derived Heterocycles Part I. Reductive Fission of Benzotriazoles to O-Phenylenediamines," 10 J. Chem. Soc., 1268-73 (1968) ("Burton"). Burton disclosed the following N-alkylation reaction using K_2CO_3-acetone:

[Diagram Omitted In Printing]

RX 3794; Taylor Tr. 2273-74.

9. The Branca '522 Patent

FF D 121. Based upon Dr. Baldwin's declaration, the examiner stated that the Pachter reference would have provided little if any guidance, regarding the use of DMC or its hydrochloride salt in the N-alkylations of the '035 patent using a Pachter-type base/solvent combination. The examiner stated that the equivalence of methyl iodide and DMC has not been demonstrated using the conditions of the '035, but only under the harsher conditions employed in the '257 patent. Taylor Tr. 2764-65.

FF D 122. In connection with the Order Granting Request for Reexamination, dated May 2, 1994, the examiner stated in part as follows:

> The equivalence of methyl iodide and DMC has not been demonstrated using the conditions of '035 but only where more strongly forcing conditions are employed in '257.

RX 1653.

FF D 123. Dr. Taylor's opinion is that prior art not of record before the PTO shows that using the conditions of the '035 patent, and for the purposes of alkylating TZP, methyl iodide and DMC are equivalent. Taylor Tr. 2764-65.

FF D 124. U.S. Letters Patent 4,377,522, issued to Quirico Branca in 1983, is prior art based on its filing date before the Japanese counterpart to the '035 patent. The examiner did not have the '522 patent during the reexamination of the '035 patent. RX 1657; Kende Tr. 1312.

FF D 125. The '522 patent discloses the alkylation of a seven member ring N-aryl amide using potassium carbonate/acetone and the alkylating agents DMC, DEC, or methyl iodide. Taylor Tr. 2757-59; Kende Tr. 1311-13; RX 1657; RPX 1091.

FF D 126. Branca '522 discloses the alkylation of a seven member ring lactam using DMC with a weak inorganic base, such as alkali metal carbonate (*e.g.*, potassium carbonate) in a solvent such as a (*e.g.*, acetone). Kende Tr. 1315-16; Taylor Tr. 2755-56; RX 1657; RPX 1095.

FF D 127. Branca is a N-aryl amide seven-membered ring structure, a benzodiazepine. It is a seven-membered ring benzodiazepinone where the N-aryl amide linkage is the same as it is in TZP. Taylor Tr. 2755-56.

FF D 128. RPX 1027, 1019, 1091, and 1092 are all examples of benzodiazepines. Gokel Tr. 1012-14.

FF D 129. Benzodiazepines are related to benzothiazepines in that they have a six member ring fused to a seven member ring and they have the amide, however, they lack the sulfur. Gokel Tr. 1014.

FF D 130. The Branca '522 patent discloses an alkylation reaction of a seven member ring N-aryl amide using DEC, DMC or methyl iodide with potassium carbonate and acetone. Kende Tr. 1311-1316; Taylor Tr. 2757-58; RPX 1095.

FF D 131. The Branca patent provides an example of the kind of art the examiner said was not before him, showing the equivalence of methyl iodide and DMC. Branca provides an example of a substrate similar to TZP

that is alkylated under '035 conditions with a dialkylaminoethyl halide and methyl iodide. Taylor Tr. 2759.

FF D 132. Prior to the alleged invention of the '035 patent, Burton (RX 3794), Fischli (RX 2130), Branca (RX 1657), Bebenburg (RX 1655), Nagarajan (RX 3820) and Nadzan (RX 3834) disclosed the use of the '035 base-solvent combinations to alkylate N-aryl amides. Taylor Tr. 2773-74.

10. The Bebenburg '887 Patent

FF D 133. U.S. Letters Patent 3,910,887, which issued to Walter von Bebenburg in 1975, was not of record during the reexamination on the '035 patent. It discloses a seven member N-aryl amide ring alkylation using DMC as the alkylating agent, and potassium carbonate/acetone as the base/solvent combination. Kende Tr. 1313-14; Taylor Tr. 2757-58; RX 1655; RPX 1092.

FF D 134. The '887 patent suggests that one can N-alkylate a seven-membered ring using methyl iodide or DMC and a base/solvent of potassium carbonate/acetone. Kende Tr. 1313-14; Taylor Tr. 2761-63; RX 1655; RPX 1092.

11. The '338 Schenker Patent

FF D 135. U.S. Letter Patent 3,644,338, which issued in 1972 to Karl Schenker, is not of record in the reexam. *See* Taylor Tr. 2747. Schenker discloses the alkylation of a compound which, although not an aryl amide, is an amide with a seven-membered ring. The reaction uses

DMC as one of the possible alkylating agents, potassium carbonate as a possible base, and acetone as a possible solvent. Taylor Tr. 2747-49, 2751, 2754; RX 1656; RPX 1095.

FF D 136. The Schenker substrate has the nitrogen and the carbon double bond oxygen reversed in position from that of an N-aryl amide, so now the [C] double 10 group is attached to the aromatic ring and the nitrogen is not. The substrate is called a benzamide, which is an amide. Taylor Tr. 2747.

FF D 137. Dr. Pachter testified that benzamides were substrates with which his conditions did not always work. Taylor Tr. 2747-48.

The Schenker patent teaches that:

> The reaction is advantageously performed in the presence of a solvent such as a polar solvent, for example in a lower alkanol such as methanol or ethanol or in a lower alkanone such as acetone and especially in the presence of a condensing agent such as a weak inorganic base such as sodium or potassium carbonate, or in weak organic base such as a tertiary amine. . . .

Taylor Tr. 2749; RX 1656; RPX 1095.

FF D 138. The solvents referred to in Schenker are the kind of solvents that are capable of solvating potassium, such as a polar solvent. Taylor Tr. 2749.

FF D 139. Schenker also teaches that one should avoid strong bases (such as those found in the '257 patent) because their use results in low yields. Taylor Tr. 2749-50; Kende Tr. 1315-16; RX 1656.

FF D 140. Example 2 of Schenker discloses finely grounded potassium carbonate in acetone, with DMC·HCl. Taylor Tr. 2751-52; RX 1656.

FF D 141. Example 5 of Schenker discloses finely ground potassium carbonate in acetone, with DMC·HCl. Taylor Tr. 2752-53; RX 1656.

FF D 142. Abic's expert is of the opinion that Schenker is closer art to the '035 patent than the Nagarajan article. Schenker discloses the same base/solvent combination and alkylating agent disclosed in the '035 patent, whereas Nagarajan used sodium hydroxide (a different base) and acetone in a homogenous solution. Taylor Tr. 2754-55.

FF D 143. Abic's expert is of the opinion that Schenker is closer to the '035 patent than any reference of record. Taylor Tr. 2754-55.

12. The Krapco [sic] '006, '889, '967 and '902 Patents

FF D 144. The '006 and '889 patents, which contain an identical Example 1B, teach the N-alkylation of benzothiazepinones using sodium hydroxide and toluene in a system that generates water. RX 3669; RX 3673; Taber Tr. 2160; Gokel Tr. 886-93; RX 4038C; Kende Tr. 1430-31.

FF D 145. The reaction described in Example 1B of the '006 and '889 patent is illustrated as follows:

[Diagram Omitted In Printing]

RPX 3673A; Gokel Tr. 887.

FF D 146. An organic chemist of ordinary skill back in 1980-81 would have recognized that the N-alkylation reaction in Example 1B of the '889 and '006 patents was carried out in a hydrous system as opposed to an anhydrous system. This is true even if "great pains" were taken to dry the toluene, glassware and other equipment of the reaction system. RX 4038C.

FF D 147. The starting material in Example 1B of the '006 and '889 patents contains a phenyl group at the two position of the benzothiazepine molecule, and column 1 of those patents also describes a methoxyphenyl at the two position, which is the identical substituent contained at the two position of TZP. Taber Tr. 2161; Gokel Tr. 888.

FF D 148. Dr. Baldwin believes that if TZP was used as the starting material in the N-alkylation process of Example 1B of the '006 and '889 patents, that process would be equivalent to the process of the '035 patent. RX 4038C.

FF D 149. Dr. Baldwin doesn't "know one way or the other" whether a chemist with the '889 patent in front of him would have tried the reaction in Example 1B with TZP. Dr. Baldwin agreed that "[i]t is a possibility" that the chemist would have tried the reaction with TZP, having seen that the starting substrate in Example 1B was "analogous" to TZP. RX 4038C.

FF D 150. The following question and answer occurred at Dr. Baldwin's October 6, 1994 deposition:

> Q So if you had a series of reactions in which various analogous substrates were treated with the same reaction conditions, same base, same solvent, same alkylating agent,

same temperature, same stirring conditions, then you would be able to hazard a guess as to what another one of the set of analogous structures would do under the same conditions?

A I think you might be in a position to make some guesses, yes.

RX 4038C

FF D 151. The reaction disclosed in Example 1B of the '889 and '006 patents would involve the aziridinium ion as the alkylating agent. Gokel Tr. 895; RX 4038C; Taylor Tr. 2775.

FF D 152. The reaction system in Example 1B of the '006 and 889 patents is a "reversible" reaction system. RX 4038C.

FF D 153. The alkylating agent used in Example 1B of the '889 and '006 patents, dimethylaminoethyl hydrobromide, is one of the alkylating agents encompassed by claim 1 of the '035 patent, specifically because claim 1 of the '035 patent broadly states "dimethylaminoethyl halide." Gokel Tr. 888; RX 4038C.

FF D 154. Example 1B in the Krapcho '889 and '006 patents is illustrated on RPX 3669A showing the alkylation of a benzothiazepinone using sodium hydroxide and toluene as the base/solvent. The patents identify the bases as alkali metal hydroxides. Taber Tr. 2160.

FF D 155. The substrate in Example 1B of the '889 and '006 patents has a benzene group bonded to the 2 position. However, column 1 of the patents contemplates

a methoxyphenyl at the 2 position, just as in TZP. Taber Tr. 2161.

FF D 156. Example 1B of the '889 and '006 patents teaches that the alkylating agent used in the N-alkylation reaction was sufficiently stable under the hydrous reaction conditions to alkylate the benzothiazepinone substrate and obtain a yield of N-alkylated product. Gokel Tr. 896; RX 4038C.

FF D 157. The '902 patent describes the use of sodium hydroxide and toluene in a hydrous system for the N-alkylation of a 2,3-dihydrobenzothiazepinone. RX 3647; Taber Tr. 2161-62.

FF D 158. The N-alkylation reaction described in Example 4 of the '902 patent may be illustrated as follows:

[Diagram Omitted In Printing]

FF D 159. The Krapcho '902 patent, example 4, describes N-alkylating the N-aryl amide of a benzothiazepinone with an aminopropyl halide with sodium hydroxide and toluene. Taber Tr. 2161; RPX 3647.

FF D 160. The substrate in example 4 of the '902 patent is a 2,3-dihydrobenzothiapinone, like the structure of TZP. Taber Tr. 2161-62.

FF D 161. In order to get a retro-Michael side reaction using the substrate of example 4 of the '902 patent, the proton would have to be removed at either the 2 or 3 position. However, the protons at 2 and 3 are not sufficiently acidic to remove even under the extreme conditions of sodium hydroxide and toluene. Taber Tr. 2163-63.

FF D 162. Nothing in the '902 patent suggests that side reactions will occur during N-alkylation. Taber Tr. 2162-63.

FF D 163. The '967 patent teaches the use of an "alkali metal hydroxide" in combination with toluene to N-alkylate a 2,3-dihydrobenzothiazepinone using dimethylaminoethyl chloride (DMC) as the alkylating agent. An alkali metal hydroxide would include sodium hydroxide or potassium hydroxide. RX 3632, RX 3125; Taber Tr. 2159-60, 2162; Gokel Tr. 870-72, 877-78, 881.

FF D 164. The general Formula II of the '967 patent includes the following 2,3-dihydrobenzothiazepinone (shown in the '967 N-alkylation reaction):

[Diagram Omitted In Printing]

RPX 3125A, RX 1125; Gokel Tr. 879-81; Taber Tr. 2158-60.

FF D 165. The substrate for the N-alkylation reaction of the '967 patent differs from TZP (the substrate of the '035, '257, and the accused processes) only by the substitution of hydrogen (H) for hydroxyl (OH) at the 3 position of the TZP molecule. Taber Tr. 2159; Gokel Tr. 881; RPX 3125A.

FF D 166. Stereochemistry is the disposition of atoms and molecules in three dimensional space (as compared with a two dimensional piece of paper). Kende Tr. 1175. Claim 1 of the '035 patent does not refer to stereochemistry. Gokel Tr. 882; Taber Tr. 2177; CX 1.

FF D 167. At page 7 of his declaration submitted to the PTO during the Reexamination, Dr. Baldwin argued that subjecting TZP to basic conditions might have destroyed the "stereochemical" integrity of the molecule.

Dr. Baldwin stated that such stereochemistry in diltiazem is critical to its pharmacological activity. RX 1658.

FF D 168. The definition of the alkylating agent provided in the '967 patent includes dimethylaminoethyl chloride (DMC). RX 3125; Taber Tr. 2159; Gokel Tr. 877-78.

FF D 169. All of the examples of the '967 patent describe the use of toluene as a solvent for N-alkylation. RX 3125; Taber Tr. 2159; Gokel Tr. 872.

FF D 170. The reaction drawn on poster RPX 3125A is "a reaction in which water would be produced," specifically, by the hydroxide ion of sodium hydroxide reacting with the hydrogen ion attached to the nitrogen on the benzothiazepinone substrate. In addition, if the hydrochloride salt of DMC was used as the alkylating agent in the N-alkylation reaction, as disclosed as a possible alkylating agent in the '967 patent, two molecules of water would be produced for each molecule of alkylated product. Gokel Tr. 882-83.

FF D 171. The N-alkylation reaction disclosed in the '967 patent, using alkali metal hydroxide as the base, is hydroxide mediated, just as complainants' expert, Dr. Gokel, testified that the N-alkylation step of the Profarmaco process, using sodium carbonate as the base, also is hydroxide mediated. Gokel Tr. 709, 882-83; Taylor Tr. 2775.

FF D 172. "Hydroxide-mediation" means that the hydroxide ion carries out the conversion of TZP to its anion, in contrast to when carbonate ion acts as the base to convert TZP to its anion. Taylor Tr. 2775.

FF D 173. Complainants' expert, Dr. Gokel, would agree that the Profarmaco process is an N-alkylation process practiced with a benzothiazepinone and 2-dimethylaminoethyl hydrochloride in the presence of sodium carbonate in a mixture of toluene and water. The sodium carbonate undergoes a reaction to produce sodium hydroxide, thus making the N-alkylation reaction in the Profarmaco process hydroxide mediated, as is the N-alkylation process disclosed in the '967 patent. RX 3125; Gokel Tr. 709m 882-83; Gokel Witness Statement.

FF D 174. Complainants' expert, Dr. Gokel, does not recall whether the '967 patent discloses any warnings or precautionary statements that the alkylating agent, DMC, would be unstable in a hydrous system containing sodium hydroxide or potassium hydroxide. Nor does he recall the '967 patent containing any warning or precautionary information about the possibility of a retro-Michael reaction using a hydrous system in the presence of sodium hydroxide or potassium hydroxide. Nor does he recall whether the '967 patent contains any warning or precautionary information about the possibility of alkylation of the amide oxygen when using sodium hydroxide or potassium hydroxide in a hydrous system. RX 3125; Gokel Tr. 884-85.

FF D 175. In the N-alkylation reactions described by Krapcho in the '967, '889, '006, and '902 patents, each of which occurred in hydroxide bases under hydrous conditions, no hydrolysis of the amide bond was reported. Taber Tr. 2165.

FF D 176. The N-alkylation reactions disclosed in the Krapcho '967, '889, '006 and '902 patents are hydrous

reactions, for at least two reasons. First, when the base, sodium hydroxide, deprotonates TZP, water is produced. Second, hydrogen chloride or hydrogen bromide from the alkylating agent will react with the sodium hydroxide to produce water. Taber Tr. 2163; Kende Tr. 1430-31; Taylor Tr. 2776.

FF D 177. None of the Krapcho patents contains any comment regarding possible negative side-reactions. Taber Tr. 2165.

FF D 178. There is no suggestion or warning in the '967 (RX 3125), '889 (RX 3673), '006 (RX 3669), or '902 (RX 3647) Krapcho patents, which disclosed N-alkylation of benzothiazepinones in hydrous reactions, that amide carbonyl O-alkylation would occur under hydrous conditions using sodium hydroxide and toluene. Taber Tr. 2163-64.

FF D 179. The Krapcho patents (U.S. Letters Patent 3,895,006; U. S. Letters Patent 3,948,889; U.S. Letters Patent 3,075,967; U.S. Letters Patent 3,455,902) describe the N-alkylation of benzothiazepinones. Taber Tr. 2168; RX 1233, 1375, 1609.

FF D 180. TZP is a 2,3-dihydrobenzothiazepinone. Taber Tr. 2162.

FF D 181. The subject matter of the Krapcho patents has "to do with the alkylation of benzothiazepinones in general." RX 4038C.

FF D 182. During the reexamination of the '035 patent, the examiner relied upon the testimony of Dr. John Krapcho, which was included in Tanabe's response to the November 18, 1994 Office Action, stating:

> Dr. Krapcho is virtually the founder to the entire field of 1,5-Benzothiazepine-4-ones (as well as other closely related compounds . . . Contrary to requestor's argument Dr. Krapcho's testimony is seen as relevant. This relevancy is shown by the pioneering nature of Dr. Krapcho's work as evidence by the Krapcho patents of record and Reexam 90/003,044. The fact that such an expert in this field should be surprised that the process in Gaino et al. '035 should work with a dramatic and consistent increase in yields is entitled to considerable weight. If such an expert should be surprised, just how would such a process be so obvious to one or ordinary skill in the art (as requestor would have us believe)?

RX 1653 (¶¶7 and 10); Kende Tr. 1378-79.

FF D 183. Dr. Krapcho stated to the PTO that he was extremely surprised, since he had worked solely with anhydrous alkylating conditions, that alkylation could take place under hydrous conditions such as the '035. RX 1653; Taylor Tr. 2733-2734.

FF D 184. Complainants used the term "hydrous" during the Commission proceeding to include a system having a base or solvent that contains a small amount of water. Dr. Kende defined anhydrous as completely free of water and hydrous as not completely free of water. Kende Tr. 1162.

FF D 185. The Patent Reexamination Examiner expressed the opinion that if Dr. Krapcho, who is a great expert in the field of benzothiazepine chemistry, could be surprised, it is not possible that one of ordinary skill not be surprised. RX 1653; Taylor Tr. 2734.

FF D 186. Dr. Krapcho's alleged "surprise" that a hydrous (water-containing) as opposed to an anhydrous system could be used for the N-alkylation of a benzothiazepine played an important and decisive role in the Reexamination Examiner's decision. RX 1653; Kende Tr. 1379; Taylor Tr. 2733.

FF D 187. Dr. Krapcho did not specifically bring any of his patents to the attention of the patent examiner during the reexamination proceeding. RX 3048C.

FF D 188. The Krapcho '889 patent, in particular Example 1B, would have been a useful piece of information for the patent examiner in evaluating Dr. Baldwin's representation in ¶20 of his declaration that the stability of DMC under the hydrous conditions was unpredictable prior to the '035 invention. RX 4038C.

FF D 189. The Krapcho patents taught the use of hydrous systems for the N-alkylation of benzothiazepines. Kende Tr. 1430-1431.

FF D 190. A chemist who understood the teaching of Pachter, Worley, and Nagarajan could not be surprised that N-aryl amides could be alkylated under Pachter-type hydrous conditions of potassium hydroxide and acetone or potassium carbonate and acetone. Taylor Tr. 2735.

FF D 191. In Dr. Taylor's opinion, the examiner should not have been surprised that TZP could be alkylated under hydrous conditions. Taylor Tr. 2735-2736.

FF D 192. A bench chemist may find one process that works for him and continue to use it over and over. Pachter Tr. 1541.

FF D 193. Nothing in Dr. Krapcho's work required him to change to Pachter conditions. Pachter Tr. 1542.

13. Kugita I, II, III and IV

FF D 194. In 1970, Tanabe scientists, in Kugita I, reported treating TZP with hot aqueous hydroxide to the destruction of the molecule. From the results reported in Kugita I, Profarmaco's expert concluded that the stereochemistry of TZP was not disrupted under these conditions. RX 3806; Taber Tr. 2176-77.

FF D 195. In his declaration submitted to the patent examiner during the reexamination proceeding, Dr. Baldwin started:

> [I]n Pachter, only methylation with methyl iodide is performed on non-lactam substrates. Pachter does not alkylate with any amide with the highly reactive and unstable DMC or any closely related alkylating agent. Alkylation conditions used for methyl iodide could not have been extrapolated to dissimilar alkylating agents such as DMC because of the differences in the structure stability and reactivity of the different alkylating agents.

RX 1658.

FF D 196. The examiner during reexamination found that the equivalence of methyl iodide and DMC had not been demonstrated under '035 conditions. RX 1653; Taylor Tr. 2764-2765.

FF D 197. The process of claim 1 of the '035 patent uses dimethylaminoethyl halide, such as DMC, as the alkylating agent. CX 1; Pachter Tr. 1512.

FF D 198. DMC is an alkyl halide. Pachter Tr. 1558.

FF D 199. The mechanism of alkylation is almost irrelevant to the expectation that methyl iodide and DMC will both act as alkylating agents. Differences between mechanism of alkylation with DMC and methyl iodide are not important for determining whether the '035 processes are obvious. Taylor Tr. 2704, 2710.

FF D 200. When medicinal chemists begin to develop reactions for their compounds, the first alkylating agent they usually use is the simplest alkylating agent, namely methyl iodide or methyl sulfate. This methylation reaction serves as a model. Chemists work out reaction conditions with the simplest compound possible. After working out reaction conditions, medicinal chemists then use DMC or other related alkylating agents using the same procedures as used with methyl halide to make the desired compound. Pachter Tr. 1512-13; Taylor 2704.

FF D 201. DMC is used to alkylate TZP in order to allow the compound to dissolve in water and thus enter the bloodstream either orally or by way of injection. Pachter Tr. 1513-14.

FF D 202. DMC and related alkylating agents are among the most common of side chains put on drug molecules. Thousands of examples exist in the literature of alkylation with DMC and related dialkylaminoalkyl halides. Pachter Tr. 1513-14.

FF D 203. Chemists use the same conditions for alkylating with methyl iodide and DMC, and at least for the purposes of experimentation and development, do not worry about aziridinium or loss of alkylating agent. DMC and related compounds have been used in medicinal chemistry for over 50 years. Pachter Tr. 1534-35.

FF D 204. Dr. Pachter knows of no examples related to a pharmaceutical compound where a chemist started the alkylation reaction by using methyl iodide and then switched to DMC and the desired result was not obtained. Pachter Tr. 1535.

FF D 205. Tanabe scientists first used methyl iodide as the alkylating agent followed by using DMC as the alkylating agent, both with a 20 percent excess of alkylating agent, thus indicating that Tanabe scientists believed there to be no difference between the two for the purpose of conducting test reactions. Pachter Tr. 1533-1534.

FF D 206. Using conditions other than those of the '035 patent, Kugita II (RX 3807) used methyl iodide as the alkylating agent, and Kugita III (RX 3809) used DMC as the alkylating agent. The results in these cases were comparable. Pachter Tr. 1593.

FF D 207. Eleven years before the priority date of the '035 patent, Tanabe scientists had concluded that when sodium hydride was used as a base in the N-alkylation reaction, low yields and numerous side reactions resulted. In Kugita et al., *Chem. Pharm. Bull.*, *19*(3), 595-602 (1971) ("Kugita III"), the author stated that "[r]eaction of 2-aryl-3-hydroxy-2,3dihydro-1,5-benzothiazepin-4(5-ones (I) with dialkylaminoethyl halides and dioxane using sodium hydride as a base afforded the

N-dialkylaminoalkyl derivatives (II) in low yields." Table I reported the result of numerous N-alkylation reactions, and those in which sodium hydride was used as the base, the yields were low. RX 3809.

FF D 208. The Kugita III article states that "[t]he reaction in the presence of dimethylsulfinyl carbanion and dimethylsulfoxide resulted in a remarkable increase in the yields (Table I)." RX 3809; RPX 3809.

FF D 209. During the reexamination of the '035 patent, Complainants' expert, Dr. Baldwin, submitted a declaration to the PTO in which he speculated that the following side reactions might occur (i) the so-called "retro-Michael reaction," (ii) alkylation of the amide oxygen, (iii) alkylation of the 3-hydroxyl, (iv) dehydration between that 2 and 3 position, (v) hydrolysis of the amide bond, and (vi) alkylation at the 1 and 2 positions under "certain conditions." Dr. Baldwin also speculated that dimethylaminoethyl halide alkylating agents might have been unstable under '035 conditions, thus reducing the yield of the reaction. RX 1658.

FF D 210. In a 1973 publication by Tanabe, Kugita IV, N-alkylation of TZP with DMC was reported with a very high yield, thereby indicating that no major side reactions occurred. Kende Tr. 1274-76; RX 1641; RX 1641a.

FF D 211. Kugita I (published by Tanabe in 1970), a paper of which both Drs. Baldwin and Kende were not aware, clearly shows that under aqueous alkaline conditions you do not get a retro Michael-reaction. Pachter Tr. 1520-22; RX 2148; RPX 3806A.

FF D 212. Kugita I (which cites the Mills and Whitworth retro Michael paper) were trying to see whether they could get retro-Michael like Mills using TZP – however no retro Michael occurred. Pachter Tr. 1521-22; Taber Tr. 2175-76; RX 2148; RX 2152.

FF D 213. A chemist who was aware of Kugita 1 would "absolutely not" have expected a retro-Michael reaction using Pachter conditions to alkylate TZP using DMC. Pachter Tr. 1519, 1522; Taber Tr. 2176-77; RX 2148. Dr. Taylor agrees with Dr. Pachter, "Michael – reverse Michael is a dead horse." Taylor Tr. 2704.

FF D 214. None of the Kugita papers reported a retro-Michael. Kende Tr. 1335, 1452-54.

FF D 215. In a 1970 article published by Tanabe scientists (referred to as "Kugita I") (RX 3806), Kugita et al. referred to the work of Mills and Whitworth. Tanabe scientists reported that under the conditions used by Mills and Whitworth, *i.e.*, heating TZP with aqueous sodium hydroxide until destruction of the molecule, no retro-Michael occurred with the TZP molecule. RX 3806; Pachter Tr. 1520-22; Kende Tr. 1452-54; Taber Tr. 2177.

FF D 216. Kugita I (RX 3806) taught that hydrolysis of the lactam ring can occur yet would be minor, with respect to the amount of by-product occurring. RPX 3806; Pachter Tr. 1572.

FF D 217. There was no reported retro-Michael reaction in any of the Tanabe scientific papers by Kugita. Kende Tr. 1335.

FF D 218. Tanabe scientists, in one of the Kugita papers, taught that O-alkylation occurs only after the amide nitrogen has been alkylated. Kende Tr. 1338.

14. Jarrousse

FF D 219. In a 1951, Jarrousse, "Comptes rendues des séances de l'Académie des sciences" Apr. 9, 1951, p. 1424 ("Jarrousse"), DMC is subjected to extremely harsh basic, aqueous conditions without significant decomposition. RX 2145; Pachter Tr. 1518-19.

15. Finkelstein

FF D 220. In a 1951 article by Finkelstein and Linder, Studies in Phenanthridine Chemistry" 73 J. Amer. Chem. Soc. 302-04 (1951) ("Finkelstein"), an N-alkylation procedure (previously described by Graebe and Wander, 276 Ann. 245 (1893)) was conducted under extremely harsh conditions, using DMC and a large excess of molten potassium hydroxide at 150° for five hours. A high yield was reported, and no decomposition of the DMC was reported. RX 4025; RPX 4025A; Pachter Tr. 1515-17, 1519.

FF D 221. Finkelstein based his alkylation reaction using DMC on the same alkylation reaction reported by Graebe in 1893 using methyl iodide. RX 4025; RPX 4025(A); Pachter Tr. 1516-17.

FF D 222. The Pachter conditions, used in the '035 patent, are much milder than the Jarrouse or Finkelstein

conditions, yet the reaction in both Jarrouse and Finkelstein was stable enough to produce what both investigators called "excellent yields." Pachter Tr. 1519.

16. Price and Iyer

FF D 223. The Price article (RX 3817) and Iyer article (RX 3132C), articles cited by Dr. Kende in his declaration submitted to the PTO during Reexamination, clearly teach that the aziridinium ion will be of sufficient stability and that the N-alkylation will proceed at a sufficient rate that one would have a reasonable expectation of success under the '035 conditions. Taber Tr. 2171-72.

FF D 224. In 1981, the Price (RX 3817) and Iyer (RX 3132C) articles taught that aziridinium is stable enough to allow N-alkylation without any difficulty. Taber Tr. 2173.

FF D 225. If the concentration is a tenth of what it used to be, the reaction will take 100 times as long. In Price (RX 3817), the reaction is conducted under conditions of high dilution, so one would expect that bimolecular reactions would be disfavored. Taber Tr. 2170.

17. Tanabe's KOH/DMSO Process

FF D 226. Prior to 1981, Tanabe used the base-solvent combination KOH/DMSO for the N-alkylation of TZP in the manufacture of diltiazem. RX 3607; RX 3737-C.

FF D 227. In 1981, the inventors of the '035 patent had as their goal the improvement of the commercial manufacturing process using KOH/DMSO as the base-

solvent combination in the N-alkylation of TZP. RX 3737-C; RX 3742-C.

FF D 228. The inventors hoped to obtain a yield equal to that which had been obtained with the KOH/DMSO method. RX 3742-C.

FF D 229. The inventors were also attempting to produce diltiazem having the same purity as that made by the KOH/DMSO process. RX 3739-C.

FF D 230. The problem faced by Tanabe at the time of the development of the process claimed in the '035 patent was to select a solvent which was easier to recover than the DMSO solvent used in Tanabe's existing commercial process. RX 3793-C; RX 3737-C.

FF D 231. The first change made to the KOH/DMSO process involved changing the solvent DMSO. RX 3737.

FF D 232. Acetone was the first solvent chosen by the inventors to replace DMSO. RX 3739.

FF D 233. Potassium hydroxide was the very first base selected as an alternative when Tanabe began to scale up production from the KOH/DMSO process. RX 3793-C.

FF D 234. More than one year prior to the filing of the application for the '035 patent (beginning in 1973), Tanabe manufactured diltiazem using a trade secret process which used KOH as the base and DMSO as the solvent. During this time period, Tanabe sold the diltiazem into a number of countries, including the United States. RX 3607; CX 646.

FF D 235. During reexamination of the '035 patent, Tanabe submitted to the PTO declarations of alleged patent law experts, including that of James Gambrell, Esq., in support of its position that Tanabe's KOH/DMSO process was not prior art to the '035 patent. During the course of preparing his declaration, Mr. Gambrell communicated with Pennie & Edmonds and deleted certain material from his draft declaration. Specifically, Mr. Gambrell deleted the final underlined sentence in the following paragraph:

> It is my opinion that the public use and on sale sections of 35 U.S.C. § 102(b) are limited by the statutory term *'in this country.'* Therefore, the language of § 102(b) does not include the practice of a process in a foreign country (whether secret or otherwise) as prior art. *However, this is not necessarily true if the product produced by the foreign process is used or sold in the United States without restriction. In re Caveney,* [761] F.2d 671 (Fed. Cir. 1985) (emphasis added).

This sentence and the accompanying citation was apparently deleted between August 19, 1993 and August 24, 1993.

FF D 236. Potassium hydroxide (KOH) is one of the bases claimed in the '035 patent. CX 1.

FF D 237. Tanabe argued to the examiner during the reexamination that the '035 patent was distinguishable from the prior art because, *inter alia,* it was a hydrous rather than anhydrous system. RX 1638; RX 4038C.

FF D 238. The production of diltiazem using the base-solvent combination KOH/DMSO is a hydrous system. Kende, Tr. 1386-87.

FF D 239. During the time Dr. Baldwin was present at the interview with the patent examiner, the examiner was never told about the KOH/DMSO process. RX 4038C. The examiner also was not told during the interview that Tanabe regarded alkylation processes that used bases and solvents other than those specifically identified in the '035 patent to be equivalent to those in the '035 patent. RX 4038C.

FF D 240. During reexamination of the '035 patent, the examiner was presented with about 172 prior art references. RX 1603.

FF D 241. Rather than expressly disclosing the KOH/DMSO process to the Examiner during Reexamination, Tanabe submitted a book, entitled, *Diltiazem from Birth to Today*, that contained over 250 pages, of which one sentence on one page referenced the KOH/DMSO process. That page (RX 1104, page 33) was not pointed out to the Examiner. RX 1087; RX 1690; Taylor Tr. 2767-2768.

FF D 242. In the "Information Disclosure Statement Under 37 C.F.R. §1.555," submitted to the PTO by Tanabe's counsel, Tanabe requested that the Examiner take particular note of specified patents and publications. The book *Diltiazem form Birth to Today* was not one of those references. RX 1087.

FF D 243. The one page of *Diltiazem from Birth to Today* reads in pertinent part as follows:

> The N-alkylation of the lactam was also studied through close collaboration between the Organic Chemistry Research Laboratory, Onoda Factory and the Pharmaceutical Technics Division. They

> found that the reaction proceeds easily by the use of potassium carbonate and ethyl acetate in place of potassium hydroxide and dimethylsulfoxide. These two improvements were accomplished at the same time that diltiazem was being introduced overseas and greatly contributed to a plan for a plant with increased output and more efficient production.

RX 1104.

FF D 244. The passage from *Diltiazem From Birth to Today* even if found by the Examiner would not have revealed the significance of the KOH/DMSO process in particular that the process was a hydrous process. Taylor Tr. 2795-2796.

FF D 245. That sentence from *Diltiazem From Birth to Today* does not disclose that the material made by the KOH/DMSO process had been imported into the United States. Rather it leaves the impression that Tanabe was building a plant for potassium carbonate/ethyl acetate to make the compound to send to the United States. Taylor Tr. 2770.

FF D 246. The passage from *Diltiazem From Birth to Today* found on page 33 of RX 1104 does not explain that the KOH/DMSO process, like the '035 process, was hydrous. Taylor Tr. 2770-2771.

FF D 247. As a matter of PTO practice, the placement of Examiner's initials next to a cited reference indicates that the reference was expressly considered by the examiner. Manual of Patent Examining Procedure ("MPEP") § 609.

FF D 248. Examiner Bond placed his initials next to the reference, *Diltiazem From Birth To Today.*, which specifically discloses Tanabe's prior KOH/DMSO process. CX 638A.

FF D 249. Without knowing what he was looking for, Dr. Taylor believes that the one page (RX 1104) would have been extremely difficult to find. Taylor, Tr. 2768-2769.

FF D 250. Yields obtained by KOH/DMSO and KOH/acetone were "about the same." RX 3742. *See* Nakao Tr. 378-79; 398-99.

FF D 251. A May, 1981 Tanabe report stated that the yield using the KOH/DMSO method was [C]. RX 3327; Nakao Tr. 398-99.

FF D 252. In 1981, the inventors of the '035 patent sought to find a solvent to replace DMSO because it was difficult to recover. They kept KOH as the base and quickly settled on acetone. RX 3739.

FF D 253. In May 1981, Messrs. Iijima and Gaino reported that the reaction using acetone as a solvent proceeds to the same degree as it does using DMSO. RX 3314. In June 1981, Messrs. Iijima, Nakao and Gaino reported that "alkylation can take place in the same manner when KOH/DMSO is replaced with KOH/acetone." RX 3361.

FF D 254. During the Reexamination of the '035 patent, complainants also did not inform their expert, Dr. Baldwin, about Tanabe's KOH/DMSO process. Dr. Baldwin first learned about the KOH/DMSO process in May

1994, four months after he had prepared and signed his declaration. RX 4038.

FF D 255. Assuming the KOH/DMSO process was conducted under hydros conditions – which it was – Dr. Baldwin agreed that it was relevant to his declaration. RX 4038C.

FF D 256. Dr. Baldwin believes that the patent examiner would have wanted to know that Tanabe had used the KOH/DMSO process for a number of years prior to the '035 process. RX 4038C.

FF D 257. If Dr. Baldwin had known about the KOH/DMSO process, he would have told the patent examiner about it. RX 3048C.

FF D 258. The base-solvent combination KOH/DMSO is a heterogenous system. Kende, Tr. 1355-56. The '035 system is also heterogeneous. Taylor, Tr. 2613.

FF D 259. The KOH/DMSO system used by Tanabe for the commercial manufacture of diltiazem falls somewhere between '257 and '035 conditions in terms of reactivity. The KOH/DMSO system thus falls in the middle of the reactivity of compounds tested by Dr. Pachter. Thus, in Dr. Pachter's opinion, because KOH-DMSO and '257 conditions succeeded, so should '035 conditions. Pachter, Tr. 1537.

FF D 260. Both the KOH/DMSO process and the '035 process use the TZP substrate, the base and solvent of the KOH/DMSO process are interchangeable with the '035 bases and solvents, DMC and the aziridinium ion are present in both the KOH/DMSO process and the '035 process, water is present in the KOH/DMSO process and

the '035 process, and the KOH/DMSO process and the '035 process are hydroxide mediated. RPX 1153; Taylor, Tr. 2774-77, 2791-92.

FF D 261. The KOH/DMSO process and the '035 process work in the same way. Taylor, Tr. 2793-2794.

FF D 262. Tanabe sold DMC•HC1 produced using the KOH/DMSO process to MMD in the United States pursuant to various supply agreements from approximately 1976 through approximately 1984. Fogel Tr. 71-72; Joint Stipulation Nos. 22-26.

FF D 263. MMD received formal FDA approval to market its first DZM-HC1 Cardizem® products to the general public in or about November 1982. RX 1249.

FF D 264. Given the '257 patent, Pachter, and the KOH/DMSO process, one would have been 98% certain of success using Pachter conditions on TZP since the KOH/DMSO process showed success using the identical substrate under aqueous KOH basic conditions with no side reactions. Pachter Tr. 1536-37; Taylor Tr. 2703, 2766-67.

C. Additional Findings Concerning Side Reactions

FF D 265. In their declarations submitted to the PTO during the Reexamination of the '035 patent, Drs. Baldwin and Kende described the retro-Michael reaction pointing out that the first step of the retro-Michael reaction involves removal of a hydrogen atom from the carbon at the 3-position. RX 3132; RX 1658.

FF D 266. The retro-Michael reaction shown by Drs. Baldwin and Kende in their declarations occurs in a molecule which, unlike TZP, does not have a hydroxyl group at the 3-position. RX 3132; RX 1658; RPX 4030; Taber Tr. 2174.

FF D 267. For the retro-Michael to proceed, a base would have to remove the hydrogen from the carbon at position 3. Tabor Tr. 2175.

FF D 268. The presence of the hydroxyl at the 3 position renders the hydrogen atom at the C-3 position difficult to remove (non-acidic). Taber Tr. 2175.

FF D 269. The proton of the hydroxyl group attached at the C-3 position of TZP is much more acidic than the proton directly bonded to the carbon at the C-3 position. Taber Tr. 2175; RX 3048C.

FF D 270. If retro-Michael were going to occur, it should have occurred under '257 conditions. Taber Tr. 2175.

FF D 271. In the '257 patent where there is a 3-hydroxyl group on TZP, there is no reported retro-Michael reaction. Kende Tr. 1332; 1401-02; RPX 2011A.

FF D 272. In order for the retro-Michael reaction to occur, the base would have to ignore the more acidic amide NH and 3-OH and find the much less acidic 3-CH, remove the hydrogen and kick out the S minus. This on its face is unlikely. Taber Tr. 2175.

FF D 273. The prior art taught one of skill in the art how to avoid a retro-Michael reaction under '257 conditions. Kende Tr. 1335.

FF D 274. The only two references complainants rely on for the possibility of a retro-Michael reaction are (1) Mills and Whitworth and (2) Krapcho, Spitzmiller and Turk reference. Kende Tr. 1330; RX 1658; RX 2152, RPX 1009.

FF D 275. In Mills and Whitworth no alkylating agent was present, Pachter conditions were not used, and 10% potassium hydroxide dissolved in ethanol and water was used. Kende Tr. 1330-32; RPX 1011; RPX 1009; RX 1658.

FF D 276. In 1963, the Krapcho prior art avoided the retro-Michael reaction by the use of dimethylaminoethyl bromide as the alkylating agent. RX 3788; Kende Tr. 1334-35; Pachter Tr. 1583-1584.

FF D 277. In subsequent patents, such as the '967 and '902 patents, Dr. Krapcho described the N-alkylation of 2,3-dihydrobenzothiazepinones using sodium hydroxide and toluene in hydrous systems without reporting a retro-Michael reaction. Taber Tr. 2163-64.

FF D 278. In internal Squibb memorandums describing N-alkylation of a dihydrobenzothiazepinone (thiazesim) using sodium hydroxide and toluene, it is reported that no S-alkylated material, *i.e.*, retro-Michael, is observed. Kende Tr. 1439-42.

FF D 279. In the '257 patent, no-retro Michael reaction was reported Kende Tr. 1332; RX 1229.

FF D 280. The compound of Mills and Whitworth was significantly different from the compound of the '035 patent because the Mills and Whitworth compound did not have a hydroxy group. Kende Tr. 1451.

FF D 281. Krapcho, Spitzmiller and Turk used '257 conditions (sodium hydride/toluene) instead of Pachter conditions and only reported retro-Michael when they used the alkylating agent dimethylamino propyl chloride (which can not form an Az^+) but reported no-retro Michael when they used DMC. Kende Tr. 1333-34; RPX 1011; RX 1658.

FF D 282. Krapcho, Spitzmiller and Turk reported that retro-Michael did not occur when DMC was used. Kende Tr. 1334-35.

FF D 283. However in a separate paper, Krapcho, Spitzmiller and Turk taught that if you wanted to avoid retro-Michael, one should use the alkylating agent dimethylaminoethyl bromide, instead of dimethylamino propyl chloride. Kende Tr. 1334.

FF D 284. In order to get a retro-Michael reaction, one would have to abstract a hydrogen from a carbon. Abic was not concerned with possible retro-Michael reaction on TZP. TZP has a nitrogen with a proton on it, an acidic proton with nitrogen. TZP also has a hydroxyl group. The hydroxyl is far more vulnerable to attack than a carbon group. Haber Tr. 2414-15.

FF D 285. At page 8 of his declaration submitted to the PTO during the Reexamination of the '035 patent, Dr. Baldwin speculated that a possible side reaction might have been the elimination of water (*i.e.*, dehydration) under basic conditions. He shows a side reaction in which hydroxyl at the 3 position and the hydrogen at the 2 position are removed, leaving a double bond between the 2 and 3 carbon atom. RX 1658.

FF D 286. Dr. Baldwin described a hypothetical side reaction involving alkylation at the 3-hydroxyl group at the top of page 7 in his declaration submitted to the PTO during the Reexamination. RX 1658.

FF D 287. Complainants also submitted a declaration by Dr. Kende to the PTO during the Reexamination of the '035 patent. In paragraph forty-two (42) of his declaration, Dr. Kende cited to a reference by Floyd to support complainants' theory that alkylation at the 3-hydroxyl of TZP is possible. The Floyd reference is not prior art. RX 3132; Kende Tr. 1338.

FF D 288. The '257 patent taught that alkylation at the 3 hydroxyl group did not compete with alkylation at the amide nitrogen. Taber Tr. 2173.

FF D 289. In the '257 patent, when sodium hydride and DMSO were used for alkylation, the predominant reaction was alkylation at the amide nitrogen. Kende Tr. 1449-50.

FF D 290. Alkylation at the 3-hydroxyl group was not reported in the '257 patent, Tanabe's trade secret KOH/DMSO process or the '035 patent. Kende Tr. 1401; RPX 2011A.

FF D 291. The first paragraph of the Pachter reference cites a prior reference by Fones which teaches that some compounds containing nitro groups are completely inactive under '257 conditions. RX 3770; Pachter Tr. 1502, 1524.

FF D 292. The Pachter reference reported that the nitro-substituted compound which Fones could not get to react under '257 conditions produced an 80% yield using

potassium hydroxide and acetone. Kende Tr. 1524, 1459-61; RX 3770.

FF D 293. Under '257 conditions, compounds have the reverse reactivity as under '035 conditions. The nitro compound of Pachter is the least reactive under '257 conditions. Pachter Tr. 1506-07.

FF D 294. Tanabe argued to the examiner during the reexamination that the possible side reactions set forth in Dr. Baldwin's declaration had the potential of reducing the yield. RX 1638.

FF D 295. Every reaction proceeds in less than 100 percent yield but that does not make the reaction less useful. Pachter Tr. 1572.

FF D 296. Even if side reactions occur, the reaction may still yield product. Kende Tr. 1468.

FF D 297. Dr. Baldwin agreed that even if alkylation occurred at sites on the TZP molecule other than at the amide nitrogen, the reaction process could still be very commercially important. RX 4038C.

FF D 298. The possibility of side reactions would not be determinative of the question of obviousness. If there is a functional group elsewhere in a molecule that one suspects is going to interfere, or which does interfere, you can take care of the problem by standard methods, such as protecting the functional group. Taylor Tr. 2781.

FF D 299. Even if side reactions take place one would not be deterred from trying the N-alkylation reaction. Organic chemists are flexible enough to take care of them. Taylor Tr. 2797.

FF D 300. Obviousness can be found even though yield cannot be predicted. Taylor Tr. 2781.

FF D 301. In his declaration submitted during the reexamination, Dr. Kende cited to an article by Yamawaki to suggest that O-alkylation was possible. RX 3132. Dr. Kende did not inform the Examiner that Yamawaki cites to Challis, which is a chapter in a book titled *The Chemistry of Amide*, which teaches that alkylation at the amide nitrogen can be expected. Kende Tr. 1351-53. The Chalice book (pg. 927) teaches those in the art that you can expect alkylation at the nitrogen atom (and says nothing about the oxygen atom) under basic conditions. Kende Tr. 1352-53; RPX 1012.

FF D 302. If a base is used in an N-alkylation reaction, as in the '035 patent, N-alkylation is always obtained. Pachter Tr. 1553.

FF D 303. Benzothiazepinones have been alkylated for a long time and there has never been any suggestion that alkylation occurs at the amide carbonyl oxygen. The alkylation occurs on the nitrogen where the nucleophilic reactivity is. Taber Tr. 2164.

FF D 304. The Nadzan reference relied on by complainants to show O-alkylation alkylates quinolones, not amides, under '257, not '035 conditions. Kende Tr. 1344-45; RPX 1029A.

FF D 305. Of the many alkylations reported in Clark, there was only one O-alkylation. That occurred when tert-butyl bromide was used as the alkylating agent. Tert-butyl bromide is one of the worst alkylating agents to use in that alkylation. Nevertheless, N-alkylated product was

obtained. The yield of N-alkylated product was only 3 percent. However, that was almost 3 times the amount of O-alkylated product. Taylor Tr. 2934.

FF D 306. Dr. Gokel believes that due to its rigidity, the Nagarajan substrate is more likely to undergo O-alkylation than N-alkylation. CX 606; *see* Kende Tr. 1346-48. However, Nagarajan reports no O-alkylation. Kende Tr. 1346-47.

FF D 307. Abic was not concerned with O-alkylation at the 3 carbon when it was developing its process. This was a theoretical possibility. But, knowing of Tanabe's experience with conditions such as disclosed in the '257 patent without any reports of O-alkylation occurring, the possibility of such occurrence, was negligible if at all. Haber Tr. 2415.

FF D 308. Abic was not concerned with O-alkylation at the 3 carbon when it was developing its process because Abic had an aromatic amide, in the presence of base. In Abic's view, if there were no base, O-alkylation at the 3 carbon is a possibility. If base is present, there is exclusive N-alkylation, except in the presence of silver. Haber Tr. 2416.

FF D 309. No known art exists showing the O-alkylation of a benzothiazepinone. Kende Tr. 1341-42.

FF D 310. Complainants' experts cannot give a prior art example of an O-alkylation of a any [sic] simple amide. Kende Tr. 1349.

FF D 311. At page 6 of his declaration submitted to the PTO during the reexamination, Dr. Baldwin refers to a possible side reaction involving alkylation of the amide

oxygen (at position 4). He does not discuss how this reaction would occur or under what conditions. RX 1658.

FF D 312. Dr. Kende also submitted a declaration to the PTO during Reexamination which postulated the possibility of carbonyl O-alkylation. RX 3132.

FF D 313. The amide carbonyl is the carbon double bonded to the oxygen which is adjacent to the nitrogen. Taber Tr. 2164.

FF D 314. In his declaration Dr. Kende gave no example of carbonyl O-alkylation. RX 3132; Kende Tr. 1342.

FF D 315. Both Dr. Kende and Dr. Baldwin known of no example of carbonyl O-alkylation of a benzothiazepinone. Kende Tr. 1342; RX 4038C.

FF D 316. Alkylation at the amide oxygen was not reported in the '257 patent, Tanabe's trade secret KOH/DMSO process or the '035 patent. Kende Tr. 1401; RPX 2011A.

FF D 317. Complainants cite no prior art, known to one of ordinary skill in the art, in support of their argument that a hydrolysis side reaction might occur when TZP is alkylated under Pachter conditions. *See* Kende Tr. 1336.

FF D 318. Abic was not concerned with possible hydrolysis when it was developing its process. It was known that if you take diltiazem and compounds similar to it, you have an acetyl group on the hydroxyl group of position 3. You could hydrolyze off that acetyl group by using a base such as sodium hydroxide and water, hydrolyze off of that acetate without attacking the lactam ring.

So that was known to show that this would not be a danger. Haber Tr. 2413-14.

FF D 319. Abic knew that the acetyl group could be hydrolyzed, but that reaction would not also cause hydrolysis of the amide linkage. It was also known to every organic chemist that if you have an ester (acetyl is an ester) and an amide in the same compound, the amide is fairly stable and the ester is not. This fact was published, and therefore it was known that in using such conditions, hydrolysis would not happen to any large extent. Haber Tr. 2414.

FF D 320. When hydrolysis occurred with toluene and high temperature. Abic still obtained the desired product, a 7% yield. Haber Tr. 2421-22; RX 1044.

FF D 321. Complainants admit that the art they rely on to allegedly show the possibility of a hydrolysis under Pachter conditions is not prior art. Kende Tr. 1336-38.

FF D 322. At page 9 of his declaration submitted to the PTO during the Reexamination, Dr. Baldwin illustrated the reaction involving hydrolysis of the amide bond under basic conditions. RX 1658.

FF D 323. Hydrolysis of the amide bond occurs where the hydroxide ion, which is a nucleophile, adds to the amide carbonyl breaking the carbonyl-nitrogen bond, kicking out the amide, breaking the ring. Taber Tr. 2165.

FF D 324. Complainants' expert, Dr. Kende, did not know of any prior art showing the hydrolysis of the amide bond in TZP. Kende Tr. 1336.

FF D 325. In their declarations submitted to the PTO during the reexamination, Drs. Baldwin and Kende discussed the potential instability of the alkylating agent used in the '035 patent, contending that DMC is converted to an aziridinium ion, which is subjected to hydrolysis in the presence of water. RX 1658; RX 3132; Pachter Tr. 1514.

FF D 326. Even if an alkylating agent is destroyed or undergoes hydrolysis during the course of a reaction, the situation is normally remedied by adding an excess of the alkylating agent. Gokel Tr. 896-897; Pachter Tr. 1597-1598; RX 3048C.

FF D 327. Any alkylating agent, including DMC, could react with water. For example, the halogen could hydrolyze off the chlorine to form a hydroxyl group, or, under certain conditions, the DMC could react with itself to create what has been termed a dimer. One can expect a little bit of it. However, one can provide for it. One has to change conditions in order to minimize it. For example one might add more of the material to take care of any that is lost. Haber Tr. 2416-17; 2491-92.

FF D 328. Side reactions, even if they do occur, merely reduce yield of desired product. Some, if not a significant amount, of desired product may still be produced, even with side reactions. Kende Tr. 1169, 1468.

FF D 329. Although almost every reaction known produces less than 100% yield (indicating a side reaction or by-product), that does not make the reaction any less useful. Pachter Tr. 1572.

FF D 330. The possibility of 3 hydroxyl alkylation is negated based upon the '257 patent, which teaches that the 3 hydroxyl does not compete with the 5 nitrogen. Taber Tr. 2173.

FF D 331. If one were to see side-reactions, one would expect to see them under the harsh conditions of the '257 patent. However, the '257 patent does not report any of the potential side-reactions posited by complainants. Taber Tr. 2168-69; RX 1193.

D. One of Ordinary Skill in the Art

FF D 332. The person of ordinary skill would be an industrial, process development chemist, like Dr. Piselli, rather than a discovery chemist, like Dr. Krapcho. Taber Tr. 2151-56.

FF D 333. In 1981, chemists known as "bench chemists" had different objectives than those of a "process development" chemist when developing a compound. Bench chemists had as their objective the preparation of small quantities of material, not worrying initially about yield. Once a product showed promise, it was given to process development chemists whose objective was to develop procedures that would provide a more practical synthesis. Kende Tr. 519; Pachter Tr. 1495.

FF D 334. In 1981, the field of organic process development was a sophisticated technology. Pachter Tr. 1497-98.

FF D 335. The level of ordinary skill in the art at the time of the alleged invention claimed in the '035 patent, December 7, 1981, was very high. A person of ordinary

skill in the art was a Ph.D. with process development experience. Pachter Tr. 1497-98; Kende Tr. 1150; Taber Tr. 2151-56.

FF D 336. The person of ordinary skill would be familiar with the literature of organic chemistry and would be especially familiar with the patent literature in his or her field of study. Taber Tr. 2151-56.

V. UNENFORCEABILITY

A. The Tanabe KOH/DMSO Process Is Material, and Was Intentionally Concealed

FF E 1. In September, 1993, complainants made the following admission in this proceeding: "Diltiazem prepared by Tanabe in Japan using KOH and DMSO, then a trade secret, was sold to MMD more than one year prior to the filing of the '035 patent." RX3607; Findings of Fact, Section VIII(B) (3).

FF E 2. At the time Tanabe filed its Japanese application counterpart to the '035 patent, Tanabe had used its KOH/DMSO N-alkylation process for nearly 10 years to make commercial bulk diltiazem hydrochloride which was sold, *inter alia*, to MMD in the United States. RX 1406; RX 3607C.

FF E 3. Tanabe also had drafted a patent application for the KOH/DMSO process claiming that it possessed the same advantages over the '257 patent as those ascribed to the process of the '035 patent. RX 1346C; RX 1248; RX Ct; RX 1579C.

FF E 4. The Tanabe application designated P-3348 (1) covered the KOH/DMSO process, and the application

designated P-3348 (2) covered the '035 process. RX 1586; RX 1346C; RX 1248; RX 1579C.

FF E 5. The introductory sections of the Japanese KOH/DMSO and '035 patent applications, setting forth the background of the invention, are strikingly similar, differing in only a few words. RX 1579C at 132-36.

FF E 6. The Japanese application on the KOH/DMSO commercial process described that invention, in particular the benefits derived from it, in language virtually identical to that of the '035 patent:

> The above method of the present invention uses less expensive potassium hydroxide that is easier to use compared with the conventional sodium hydride. Another advantage is that it is free from the worry of explosive accidents. It is safe and excellent for industrial use.

RX 1346; RX 1194.

FF E 7. Consequently, by December 7, 1981, when Tanabe filed its two Japanese N-alkylation applications, Tanabe was well aware that the prior commercial KOH/DMSO process had, some ten years earlier, solved the disadvantages of cost and danger of explosion ascribed to the '257 process.

FF E 8. The Tanabe KOH/DMSO process was material because in solved the disadvantages of the '257 process, because it used KOH, one of the bases of the '035 patent, on TZP, the same starting material as the '035 processes, with DMC, the alkylating agent of the '035 processes, and it was a "hydrous" process as complainants have applied that term to the processes of the '035 patent. *See* Kende Tr. 1387; Pachter Tr. 1536-37.

FF E 9. When Tanabe filed its U.S. Application for the '035 patent in December 1982, Tanabe asserted that it was the '035 base-solvent combination which solved these problems. RX 1194.

FF E 10. Tanabe intentionally withdrew its Japanese application for its KOH/DMSO process. Tanabe maintains that it did so because it wished to keep that process a trade secret. RX 1579.

FF E 11. In the reexamination of the '035 patent, Tanabe submitted to the examiner a copy of Tanabe's book *Diltiazem From Birth to Today,* which, on one page of the book, contains a brief, one-sentence reference to the secret potassium hydroxide-DMSO process. Information Disclosure Statement Under 37 C.F.R. § 1.555 and Notification of Litigation Under 37 C.F.R. § 1.565, List of References Cited by Patent Owner at 7 of 7, Ref. No. 65 of "Other References" (CX 607); CX 638A.

FF E 12. The book *Diltiazem From Birth to Today,* is not listed in the reexamination certificate. CX 637.

FF E 13. No effort was made to point out the Tanabe KOH/DMSO process referred to at p. 33 of *Diltiazem From Birth to Today.* No effort was made to point out that the Tanabe KOH/DMSO process was "hydrous," as contrasted with the "strictly anhydrous" conditions of the '257 patent. The examiner was not told that diltiazem hydrochloride made by the Tanabe KOH/DMSO process was sold in the United States many years prior to the December 1981 critical date. CX 638.

FF E 14. There is no claim limitation in claim 1 of the '035 patent regarding the order of addition of the reagents. CX 1.

FF E 15. The sale in the United States, prior to the critical date, of diltiazem hydrochloride made using the Tanabe KOH/DMSO process is not described in the Tanabe book. CX 638.

FF E 16. Having only the book, which Tanabe asserted was not prior art, the examiner had no way of learning of the prior art sales.

FF E 17. The text of *Diltiazem From Birth to Today*, including cover, index, forwards and appendices, contains some 267 pages, (Production Nos. T1877-2143), and the single reference to the potassium hydroxide-DMSO process appears on page 33 of that text (Production No. T1933), as follows:

> They found that the reaction proceeds easily by the use of potassium carbonate and ethyl acetate in place of potassium hydroxide and dimethyl suflfoxide.

RX 1690.

FF E 18. There is nothing in any of Tanabe's submissions to the PTO which expressly called page 33 of *Diltiazem From Birth to Today* to the attention of the examiner. CX 638A and 638B.

FF E 19. *Diltiazem From Birth to Today* was one of some 172 references in a September 1993 Information Disclosure Statement ("IDS"), and a November 1993 Supplemental IDS. RX1690 [RX 2193], RX 1691 [RX 2193].

FF E 20. There is no reference in *Diltiazem From Birth to Today* to the fact that the KOH/DMSO process was ever used commercially in the making of diltiazem hydrochloride for sale in the United States. RX 1690; Taylor Tr. 2770.

FF E 21. Tanabe submitted to the PTO declarations of patent experts, James Gambrell Esq. and Martin Adelman Esq., which referred generally to the process used by Tanabe which "differed from the '035 process" (Gambrell at ¶ 11) or "is not disclosed in" the '035 patent (Adelman at ¶ 9), but otherwise was not identified. Neither the Gambrell declaration nor the Adelman declaration identified the process as the commercial Tanabe KOH/DMSO process, or the fact that it was a hydrous process. RX 1560; RX 1660; CX 607.

FF E 22. Tanabe also apparently withheld the identity of its prior commercial process from its experts until after the reexamination certificate was issued. *See, e.g.*, RX 403C, page 15.

FF E 23. Complainants' expert, Dr. Baldwin, conceded that this process should have been disclosed to the PTO. RX 403C, page 335.

FF E 24. Another of complainants experts, Dr. Liotta, testified on deposition that he considered the Tanabe KOH/DMSO process to be equivalent to the process of the 035 patent. Liotta Tr. 1708.

FF E 25. Tanabe had to be aware of the significance of the KOH/DMSO process as prior art at the time of the reexamination in light of the September 30, 1993 motion

by the Fermion respondents for summary determination of invalidity based on that process. *See* RX 2001C.

FF E 26. Although certain papers from this proceeding were submitted in the reexamination, Tanabe disclosed neither the KOH/DMSO process nor the Fermion motion based on it to the PTO. *See* CX 638A, 638B.

FF E 27. Tanabe argued that "the '035 patent discloses the 'dramatic improvement' of its processes over those in the '257 patent," but did not tell the examiner that the Tanabe KOH/DMSO secret prior process had provided Tanabe with the same "dramatic improvement" and the same yield as the KOH/acetone process of the '035 patent. CX 638A (KOH-acetone yield 86.3%); RX 3327; Nakao Tr. 398-99 (KOH/DMSO yield 85%).

FF E 28. A Tanabe report from June 1981 states that "[i]t became clear that alkylation can take place in the same manner when KOH/DMSO is replaced with KOH-acetone in the reaction." RX 3361.

FF E 29. Another Tanabe report from 1981 states that "[n]ormally DMSO is used as a solvent, however, the reaction proceeds to the same degree (y. 70 - 86%) with acetone. Acetone is considered advantageous since the reaction fluid has a light coloring, and the collection and disposal of the solvent is simple." RX 3328.

FF E 30. Tanabe repeatedly argued that the solvent systems disclosed and claimed in the '035 patent were hydrous and directly contrary to the strictly anhydrous systems of the '257 patent, yet Tanabe did not tell the examiner that the secret prior process also was hydrous. CX 638A; RX 1658; RX 4038C; Kende Tr. 1386-87.

FF E 31. Tanabe also asserted that "[t]o [Dr. Krapcho] the aqueous processes of the '035 patent that resulted in a 90 percent yield were 'a total surprise' and 'violated all that [he] knew.' " Yet, Tanabe did not tell the examiner that the prior Tanabe KOH/DMSO process was aqueous. CX 638A.

FF E 32. Tanabe argued that "the chemoselective alkylation of the processes of the '035 patent is critical to the industrial scale production of diltiazem," while failing to advise the examiner that the same chemoselective alkylation was possessed by its prior process for the "industrial scale production" of diltiazem hydrochloride, which was then sold in this country prior to the critical date. CX 638A.

FF E 33. Tanabe's counsel sent a draft declaration to James Gambrell, Esq., which stated that diltiazem manufactured by Tanabe in Japan by a trade secret process was sold or provided free of charge to MMD for the purposes of obtaining FDA approval, and *inter alia,* included the following paragraphs:

> 4. It is my opinion that the public use and on sale sections of 35 U.S.C. § 102(b) are limited by the terms *"in this country"*, which is in the text of the statute. Therefore, the language of § 102(b) does not include the practice of a trade secret process abroad as prior art, since such a practice is not *"in this country"*. In my opinion, this is true, even if the product from that process has been shipped to the United States.
>
> 5. For these reasons, it is my further opinion that the trade secret process used by Tanabe in

> Japan to manufacture diltiazem which was supplied to MMD, is not a public use or sale of the process "in this country," within the meaning of 35 U.S.C. § 102(b) and/or § 103.
>
> 6. Thus, it is my opinion that Tanabe's trade secret process is not prior art to United States Patent No. 4,438,035 under 35 U.S.C. § 102 and/or § 103.

RX 1694.

FF E 34. Gambrell revised his declaration, and changed the paragraphs quoted above to read as follows:

> 4. It is my opinion that the public use and on sale sections of 35 U.S.C. § 102(b) are limited by the statutory term *"in this country."* Therefore, the language of § 102(b) does not include the practice of a process in foreign county [sic] (whether secret or otherwise) as prior art. However, this is not necessarily true if the product produced by the foreign process is used or sold in the United States without restriction. *In re Caveney,* 751 F.2d 671 (Fed. Cir. 1985).
>
> 5. It is my opinion that the process used by Tanabe in Japan to manufacture diltiazem which was supplied to MMD for the purpose of seeking FDA approval would not be a public use or sale of the process or its product within the meaning of 35 U.S.C. § 102(b) and or § 103 under the principles outlined in *TP Laboratories v. Professional Positioners, Inc.,* 724 F.2d 765 [sic] (Fed. Cir.), *cert. denied,* 469 U.S. 826 (1984).
>
> 6. . . . .

RX 1694.

FF E 35. Gambrell revised his draft of the declaration. He modified but retained a paragraph stating his understanding that diltiazem was sold or provided free of charge for the purposes of obtaining FDA approval. However, he deleted, among other things, the citation to *In re Caveney*, and the sentence immediately preceding the citation. Thus, his declaration now stated that "the language of § 102(b) does not apply to the practice of a process in a foreign country (whether secret or otherwise); hence it cannot be prior art against a U.S. patent."

Therefore, his declaration contained a statement of the law that he and Tanabe counsel knew to be overly broad. Gambrell deleted the caveat (that he had written and sent to Tanabe's counsel) which had immediately followed, which stated that "[t]his is not necessarily true if the product produced by the foreign process is used or sold in the United States without restriction and claims covering the same product have been granted in a U.S. patent," with citation to Federal Circuit authority in *In re Caveney*. His declaration now left the erroneous impression that products manufactured overseas are outside the purview of section 102(b), regardless of whether their distribution in the United States was experimental or commercial. Facsimile of Jim Gambrell to Lori Gentile, dated Aug. 24, 1994 (8:51 a.m.) (marked with deletions and additions). RX 1694.

FF E 36. A copy of the August 24 revision of his declaration was sent by facsimile to James B. Gambrell at the Regal Royale hotel in New York City, where he was staying in room 2312.

FF E 37. A final declaration was prepared, attached to a curriculum vitae, and executed by James B. Gambrell. The declaration was forwarded to counsel for complainants with a cover letter stating, *inter alia*, as follows:

> Please let me know if this satisfies your needs for submission to the Patent Office. As you can tell, I have changed it in some respects as I told Lori Gentile as much on Friday when I spoke with her.

RX 1694.

FF E 38. Complainants' counsel submitted the Gambrell declaration without mention of the controlling Federal Circuit authority, *In re Caveney*, or the original view of its expert. CX 638.

FF E 39. The declaration of Martin J. Adelman states that it is his understanding that Tanabe sold or provided free of charge the diltiazem made by the Tanabe KOH/DMSO process from approximately 1976 to approximately 1983. CX 607.

B. Pattern of Misconduct

FF E 40. Tanabe distinguished the '035 process from that of the '257 patent on the grounds that the processes of the '035 patent were "aqueous, which is diametrically opposed to the anhydrous systems of the '257 patent. . . ." CX 638A; RX 2193 [RX 2205].

FF E 41. Tanabe also represented that Dr. Krapcho used only anhydrous processes, while concealing from the examiner the fact that Krapcho used alkali metal hydroxides as bases in combination with aprotic solvents,

a system which complainants here assert is not anhydrous. CX 638A.

FF E 42. For example, Tanabe twice told the PTO that the '967 patent, which it referred to as "the Krapcho reference cited by Dr. Taylor" disclosed N-alkylations of benzothiazepines using "anhydrous" conditions; yet complainants here assert that the reference also discloses aqueous conditions. CX 638A; RX 2193 [RX 3205].

FF E 43. The '967 patent discloses the use of alkali metal hydroxides to perform the N-alkylation of a benzothiazepinone. Kende Tr. 1429.

FF E 44. The '967 patent conditions are "hydrous" conditions, as complainants use that term. Kende Tr. 1428-31; Taylor Tr. 2776; RX 4038C; RX 3632; RX 3673; RX 3669. Tanabe effectively concealed from the PTO the other Krapcho patents disclosing the use of "hydrous" conditions. CX 638A.

FF E 45. DMSO is an aprotic, water-miscible solvent. Kende Tr. 1397.

FF E 46. British Patent No. 1,106,119 ("the British '119 patent") published 1968, discloses alkali metal hydroxides generally, including potassium hydroxide, and also discloses the use of acetone-water mixtures as the solvent. RX 1136 [RX 2136, RX 3686]; RPX 1069; RPX 1154 [RX 2128, RX 3844].

FF E 47. The '967 patent discloses and claims the drug "thiazesim," a "parent" of diltiazem. RX 1249; Kende Tr. 1436-37.

FF E 48. The '967 patent which claims thiazesim also discloses that alkali metal hydroxides, a class which

includes potassium hydroxide, can be used in the N-alkylation of benzothizepines. RX 1134.

FF E 49. Tanabe's application for its '257 patent, which claims diltiazem, expressly acknowledges thiazesim as prior art. RX 1193.

FF E 50. Claims to an N-alkylation process which were presented in the application for the '257 patent were rejected by the U.S. PTO over, *inter alia*, the Krapcho '967 patent, and then cancelled by Tanabe. RX 1252 [RX 2026, RX 3345, RX 3863].

FF E 51. In March 1983, while the application for the '035 patent was pending, the European Patent Office identified the '257 patent and the '967 patent as relevant prior art to the EPO counterpart of the '035 patent. RX 1134; RX 1140; RX 1095.

FF E 52. Tanabe did not at that time, or at any time during the initial prosecution of the '035 patent, cite the Krapcho '967 patent in the PTO. RX 1195 [RX 3118].

FF E 53. The European Patent Office rejected the European application as unpatentable over the '257 patent in view of the Krapcho '967 patent. The Israeli and the Finnish Patent Offices also rejected the respective '035 counterparts as unpatentable over the Krapcho '967 patent. RX 1096 [RX 1122, RX 1344, Rx 3225], RX 1098 [RX 1123] and RX 1100 [RX 3232].

FF E 54. Inasmuch as the Tanabe patent department was not knowledgeable about the disclosure requirements of the U.S. Patent and Trademark Office, it was the

policy of Tanabe to submit all potentially relevant information to their U.S. attorneys, so that the U.S. attorneys could determine what should be disclosed. RX 1586C.

FF E 55. Tanabe did not submit the '967 patent to its U.S. attorneys. RX 1685C.

FF E 56. A Tanabe witness and inventor listed on the '035 patent, Shoji Nakajima, was unable to explain why Tanabe did not follow its general policy with respect to the '967 patent. RX 1586C.

FF E 57. Another Tanabe witness, Hisayoshi Hashimoto, testified that Tanabe did not cite the '967 patent to the PTO. He testified that Tanabe believed the '257 patent to be more relevant because it disclosed a process for the manufacture of diltiazem. RX 1583.

FF E 58. An inference can be drawn that Tanabe knew that the '967 patent was material to its '035 patent application, and intentionally withheld it.

Supposed Side-Reactions

FF E 59. The examiner stated as follows:

> The arguments concerning the possibility of side reactions . . . are not seen as having great weight in this particular case one way or another. Nor are the arguments concerning the use of DMC-HCl.

RX 1653.

FF E 60. Tanabe made at least two misleading arguments regarding side reactions. They were the arguments that ring cleavage or the retro-Michael reaction of TZP

might take place under Pachter ('035 conditions). Taylor Tr. 2723-24; Pachter Tr. 1519-20.

Ring Cleavage

FF E 61. Dr. Baldwin in his declaration submitted to the examiner, stated at paragraph 47, as follows:

> In addition, the Nagarajan reference suggested that ring cleavage was a distinct possibility under Pachter base/solvent conditions of seven-membered oxazepines (see Experimental, p. 245(d)). This too would have taught away from the processes of the '035 patent.

RX 1658.

FF E 62. In the "Conclusions" section of his declaration, Dr. Baldwin stated in part as follows:

> Fifth, British '119 and Nagarajan, viewed together, also taught the distinct possibility of ring cleavage in using a Pachter-type base/solvent system, and for this reason, would have suggested that this system be avoided in the N-alkylation reactions of the '035 patent. Indeed, when a substrate was N-alkylated which was not highly activated, the Pachter system was changed to a system similar to that of the '257 patent.

RX 1658.

FF E 63. The passage referred to by Dr. Baldwin (at ¶ 47 of his declaration) as occurring at p. 245(d) of Nagarajan does not in fact refer to Pachter base-solvent conditions, but rather to '257-type conditions of sodium amide and DMF. Kende Tr. 1369; Taylor Tr. 2720-21; 2725.

FF E 64. Complainants' attorneys submitted a letter to the PTO, in which they attempted to "amend" Dr. Baldwin's declaration, changing "Pachter base-solvent combination" to "Pachter-like base solvent combination" and changing the page reference to page 244(iii). RX 1693.

FF E 65. However, Dr. Baldwin never submitted an amended declaration to the United States Patent Office. CX 638A, 638B; Coggio Tr. 2727-28.

FF E 66. The conditions on page 244(iii) are not Pachter-like conditions either. They are not potassium hydroxide in acetone, but sodium hydroxide in dioxane, which is one of the solvents of the '257 patent. Kende Tr. 1372, Taylor Tr. 2595.

FF E 67. In fact, as Dr. Kende admitted, the ring cleavage described by Nagarajan was a reaction which one would never see with TZP. There is no connection with TZP. Kende Tr. 1367-68, 1374-5.

FF E 68. Moreover, the Nagarajan ring opening (which one would never see with TZP) occurs under '257 conditions but not under '035 conditions. Kende Tr. 1369.

FF E 69. Nagarajan expressly reported that ring cleavage occurred only with nitro-substituted N-aryl amides. Taylor 2712; Kende 1369-70; RX 1145 [RX 2155, RX 3820]; RPX 1131.

FF E 70. Moreover, Nagarajan expressly states that ring cleavage is observed under '257 conditions, but not under Pachter-type conditions. RX 1145 [RX 2155, RX 3820]; Kende 1369-70; Taylor Tr. 2726-27.

FF E 71. Dr. Kende testified that he would not have drawn any connection between the ring cleavage

reported in Nagarajan's nitro-substituted compounds under '257 conditions and the possibility of ring cleavage of TZP under '035 conditions. Kende Tr. 1367-68.

FF E 72. Nagarajan cannot be fairly read to suggest that ring cleavage was a distinct possibility under Pachter base-solvent conditions. Taylor Tr. 2728.

FF E 73. It was misleading for Dr. Baldwin to suggest to the examiner that Pachter base-solvent conditions or Pachter-type conditions led to ring cleavage. Taylor Tr. 2723, 2731.

Retro-Michael

FF E 74. Both the Kende and Baldwin declarations suggest that the possibility of retro-Michael reaction of TZP might deter chemists from attempting the N-alkylation under Pachter/'035 conditions. RX 1329 [RX 1189, RX 3112, RX 3132]; RX 1658.

FF E 75. Dr. Kende testified that an article by Mills and Whitworth suggested that retro-Michael reaction might take place with TZP. Kende Tr. 1183-1185.

FF E 76. However, Tanabe scientists published in 1970 their experiments showing that TZP did not undergo retro-Michael reaction under the same conditions which Mills and Whitworth suggested that other benzothiazepinones might undergo retro-Michael reaction. Kende Tr. 1450-1454.

FF E 77. Tanabe should have known from its own 1970 publication that there was no retro-Michael reaction of TZP under the conditions of Mills and Whitworth, and

should not have raised the possibility of such reaction as an argument to the examiner.

VI. IMPORTATION AND SALE

FF F 1. Respondent Abic manufactures diltiazem HCl in Israel and supplies it to various generic drug manufacturing companies through its subsidiary, respondent Plantex, for importation into and sale in the United States. Abic Proposed Finding of Fact 15; Complaint, ¶¶ 15-16, pp. 4-5, Exh. E.

FF F 2. Respondent Plantex is a New Jersey corporation, and a subsidiary of respondent Abic. Plantex imports diltiazem HCl and other products produced by Abic. Plantex sells in the United States the diltiazem that it imports from Abic. Plantex's Resp. to Comp. ¶22A; Abic Proposed Finding of Fact 15.

FF F 3. Respondent Fermion manufactures diltiazem HCl in Finland and supplies bulk diltiazem to respondents Interchem, Copley and Rhone-Poulenc Rorer for importation and sale in the United States. The Fermion Respondents' Prehearing Statement at 5-6.

FF F 4. Respondents Copley purchases in the United States bulk diltiazem HCl that is produced abroad by respondent Fermion and converts the bulk diltiazem into pharmaceutically acceptable forms suitable for human dosage. The Fermion Respondents Prehearing Statement at 6.

FF F 5. Respondent Interchem imports into the United States bulk diltiazem HCl produced by respondent Fermion and acts as Fermion's exclusive United

States sales representative. *See* Complaint, ¶ 20, p. 6; Exh. K.

FF F 6. Rhone-Poulenc Rorer imports diltiazem HCl into the United States obtained from respondent Fermion and converts the bulk diltiazem into pharmaceutically acceptable forms suitable for human dosage, and sells diltiazem in the United States. The Fermion Respondents Prehearing Statement at 5-6.

FF F 7. Profarmaco manufactures bulk diltiazem in Italy for importation into and sale in the United States. Russolo Tr. 1914. Profarmaco was purchased by an American company, Cambridge Corporation, shortly before the hearing. Mylan Profarmaco's Proposed Finding of Fact 6; Russolo Tr. 1913.

FF F 8. The Mylan respondents (Mylan Pharmaceuticals and Mylan Laboratories) convert the bulk diltiazem HCl manufactured by Profarmaco into pharmaceutically acceptable forms for sale in the United States. Mylan/Profarmaco's Proposed Finding of Fact 6. Complaint, ¶ 18, p. 6; Exh. D.

FF F 9. Gyma is the exclusive United States distributor for Profarmaco since January 1985. Gyma sells imported bulk diltiazem HCl to respondent Mylan. Russolo Dep. Tr. 111; Complaint, ¶ 21, pp. 6-7.

VII. DOMESTIC INDUSTRY

FF G 1. The parties have entered into stipulation of fact regarding the domestic industry. CX 728; Proposed Findings of Fact and Conclusions of Law of the Commission Investigative Staff at 122.

FF G 2. MMD's Kansas City facilities occupy over [C] square feet. CX 728.

FF G 3. Currently, MMD has over [C] square feet of its Kansas City facilities dedicated to Cardizem products made from bulk diltiazem supplied by Tanabe. Fogel Tr. 77; CX 527.

FF G 4. Hypothetically, if Tanabe changed its current process for manufacturing bulk diltiazem to Tanabe's trade secret KOH/DMSO process as practiced by Tanabe for production of diltiazem prior to 1984, or to any other process, provided that such process was appropriately qualified by MMD with the relevant regulatory authorities, MMD's manufacturing and warehousing facilities in Kansas City which are devoted to the production and storage of diltiazem products could be used, without substantial modification, to produce and store diltiazem products from bulk diltiazem manufactured by Tanabe under the KOH/DMSO process or other process. CX 728.

FF G 5. MMD has invested [C] million in plant and equipment at Roche Products, Inc. ("RPI") in Puerto Rico where Cardizem products are produced. CX 728.

FF G 6. Hypothetically, if Tanabe changed its current process for manufacturing bulk diltiazem to Tanabe's trade secret KOH/DMSO process as practiced by Tanabe for production of diltiazem prior to 1984, or to any other process, provided that such process was appropriately qualified by MMD with the relevant regulatory authorities, the plant and equipment at RPI in Puerto Rico in which MMD has invested could be used, without substantial modification, to produce and store diltiazem

products from bulk diltiazem manufactured by Tanabe under the KOH/DMSO process or other process. CX 728.

FF G 7. MMD leases [C] square feet from RPI in Puerto Rico; approximately [C] square feet are used for the production of Cardizem products. CX 728.

FF G 8. Hypothetically, if Tanabe changed its current process for manufacturing bulk diltiazem to Tanabe's trade secret KOH/DMSO process as practiced by Tanabe for production of diltiazem prior to 1984, or to any other process, provided that such process was appropriately qualified by MMD and the relevant regulatory authorities, the floor space which MMD leases from RPI in Puerto Rico for the production of Cardizem products could be used, without substantial modification, to produce and store diltiazem products from bulk diltiazem manufactured by Tanabe under the KOH/DMSO process or other process. CX 728.

FF G 9. MMD leases [C] direct labor employees from RPI; [C] of these individuals are working on the production of Cardizem CD/SR. CX 728.

FF G 10. Hypothetically, if Tanabe changed its current process for manufacturing bulk diltiazem to Tanabe's trade secret KOH/DMSO process as practiced by Tanabe for production of diltiazem prior to 1984, or to any other process, provided that such process was appropriately qualified by MMD and the relevant regulatory authorities, the direct labor employees who work on the production of Cardizem CD/SR which MMD leases from RPI in Puerto Rico could, without any substantial retraining or modification of their activities, work on the production of

Cardizem CD/SR from diltiazem manufactured by Tanabe under the KOH/DMSO process or other process. CX 728.

FF G 11. In 1992, MMD employed approximately [C] full-time associates in Kansas City, of which approximately [C] were devoted full-time to the production of Cardizem products. CX 728.

FF G 12. Hypothetically, if Tanabe changed its current process for manufacturing bulk diltiazem to Tanabe's trade secret KOH/DMSO process as practiced by Tanabe for production of diltiazem prior to 1984, or to any other process, provided that such process was appropriately qualified by MMD and the relevant regulatory authorities, the full time associates employed at MMD's Kansas facility who are devoted to full-time production of Cardizem products could, without any substantial retraining or modification of their activities, work on the production of Cardizem products from bulk diltiazem manufactured by Tanabe under the KOH/DMSO process or other process. CX 728.

FF G 13. Hypothetically, if Tanabe changed its current process for manufacturing bulk diltiazem to Tanabe's trade secret KOH/DMSO process as practiced by Tanabe for the production od [sic] diltiazem prior to 1984, or to any other process, provided that such process was appropriately qualified by MMD and the relevant regulatory authorities, the procedures for manufacturing Cardizem CD could be used, without substantial modification, for the production of Cardizem CD from bulk diltiazem manufactured by Tanabe under the KOH/DMSO or other process. CX 728.

FF G 14. Diltiazem tablets are manufactured by MMD according to the procedures set forth in CX 553C. CX 728.

FF G 15. Cardizem SR is manufactured by MMD in conjunction with Elan in Ireland according to the procedures set forth in CX 555C. CX 728.

FF G 16. MMD is a licensee of Elan under U.S. Patent No. [C] which is directed to finished dosage forms of diltiazem. CX 728.

FF G 17. Hypothetically, if Tanabe changed its current process for manufacturing bulk diltiazem to Tanabe's trade secret KOH/DMSO process as practiced by Tanabe for production of diltiazem prior to 1984, or to any other process, provided that such process was appropriately qualified by Elan and the relevant regulatory authorities, the procedures for manufacturing Cardizem SR in conjunction with Elan in Ireland could be used, without substantial modification, for the production of Cardizem SR from bulk diltiazem manufactured by Tanabe under the KOH/DMSO process or other process. CX 728.

FF G 18. Cardizem IV is manufactured for MMD by Sanofi Winthrop in the United States according to the process set forth in the NDS (CX 556C). CX 728.

FF G 19. Hypothetically, if Tanabe changed its current process for manufacturing bulk diltiazem to Tanabe's trade secret KOH/DMSO process as practiced by Tanabe for production of diltiazem prior to 1984, or to any other process, provided that such process was appropriately qualified by Sanofi Winthrop and the relevant regulatory authorities, the procedures for manufacturing Cardizem

IV in conjunction with Sanofi Winthrop in the United States could be used, without substantial modification, for the production of Cardizem IV from bulk diltiazem manufactured by Tanabe under the KOH/DMSO process or other process. CX 728.

FF G 20. On October 1, 1976, Tanabe and MMD entered into an agreement entitled Option and License Agreement. CX 728.

FF G 21. Hypothetically, it would be possible to manufacture Cardizem product formulations from bulk diltiazem made by a process other than the '035 process, given appropriate quality controls, and assurances, quantity assurances, and subject to appropriate qualification by MMD, the bulk manufacturer, and the relevant regulatory authorities. CX 728.

FF G 22. MMD does not manufacture bulk diltiazem by any process. CX 728.

FF G 23. Neither MMD nor Tanabe practices the '035 patent in the United States. CX 728.

FF G 24. Tanabe has not licensed MMD or anyone to practice the '035 patent in the United States. CX 728.

FF G 25. The claimed invention of the '035 patent was not developed in the United States. CX 728.

FF G 26. MMD's Cardizem products are made from imported bulk diltiazem that is manufactured by Tanabe at its facilities in Onoda, Japan. Fogel Tr. 68; Peterson Tr. 126; Nakao Tr. 357-358.

FF G 27. An exclusive supply agreement exists between Tanabe and MMD whereby Tanabe can only

supply bulk diltiazem to MMD and MMD can only purchase bulk diltiazem from Tanabe. Klett 240-241; CX 467; CX 728.

FF G 28. Tanabe and MMD have had a long-term exclusive supply relationship regarding bulk diltiazem. Klett Tr. 241; CX 467.

FF G 29. Diltiazem is a very short-acting product. If bulk diltiazem is administered to a patient, it would not be a pharmacologically effective [sic] because the human body would consume it too quickly. Therefore, bulk diltiazem must be formulated into dosage forms for human consumption before it can be effectively administered to patients. Kelly Tr. 164-165.

FF G 30. Cardizem products constitutes MMD's largest product line. Fogel Tr. 68.

FF G 31. Cardizem products are channel blockers which inhibit the influx of calcium into a cell. Kelly Tr. 165-166.

FF G 32. Cardizem products are taken by people who have angina (restricted blood flow in the coronary arteries) and hypertension (high blood pressure). Fogel Tr. 108; Kelly Tr. 165-167.

FF G 33. MMD's Cardizem products include Cardizem CD, Cardizem tablets, Cardizem SR and Cardizem IV which are different dosage forms of Cardizem. Fogel Tr. 68, 70-71.

FF G 34. Cardizem CD is MMD's most significant diltiazem preparation. Fogel Tr. 70.

FF G 35. A company may exploit more than one patent at a time. Burrows Tr. 2360.

FF G 36. Cardizem CD is produced in Kansas City and Puerto Rico. Fogel Tr. 69.

FF G 37. Cardizem tablets are produced in Kansas City. Fogel Tr. 70.

FF G 38. Pursuant to contractual agreements between MMD and Tanabe, MMD has been receiving bulk diltiazem from Tanabe since the late 1970's. Fogel Tr. 71-72; CX 728.

FF G 39. MMD and Tanabe have developed a relationship over the years throughout which Tanabe has consistently supplied MMD with high quality product in the quantities necessary for MMD to maintain a supply of product in the marketplace. Fogel Tr. 72; Peterson Tr. 123.

FF G 40. After MMD receives Tanabe's imported bulk diltiazem, it is sampled, tested, and released to manufacturing upon meeting specification criteria. Fogel Tr. 68-69.

FF G 41. Because of FDA requirements, MMD's processes and equipment are carefully qualified to work in combination with Tanabe's formulated bulk diltiazem. Fogel Tr. 72.

FF G 42. MMD conducts research and development related to its Cardizem products in order to comply with FDA requirements. Klett Tr. 247-248.

FF G 43. MMD cannot immediately purchase bulk diltiazem from a source other than Tanabe and produce its Cardizem preparations. Fogel Tr. 73.

FF G 44. Any change in the process for making the bulk diltiazem would require evaluation, qualification, validation, and stability tests by MMD in order to comply with FDA requirements. Fogel Tr. 72-74; Peterson Tr. 122.

FF G 45. If the process to make bulk diltiazem used in MMD's Cardizem preparations were changed, MMD would have to amend its NDA, submit a new Drug Master File to the FDA, and wait for approval, an overall process that would take somewhere between one and a half and four years. Fogel Tr. 74; Peterson Tr. 122-123.

FF G 46. Changes in Tanabe's process for manufacturing bulk diltiazem could affect MMD's final formulated Cardizem product. Tests would be necessary in order to verify any changes. Peterson Tr. 117-118, 136-137.

FF G 47. MMD could, however, change its supplier of bulk diltiazem if it made financial sense and if it did not violate an outstanding contract or supply agreement. Fogel Tr. 109.

FF G 48. From 1984-92, MMD spent over [C] million on research and development including FDA approval, clinical trials, formulation research, and research and development to support the marketing for its Cardizem products in the United States. CX 728C.

FF G 49. The pharmaceutical industry is a research and development intensive business. In addition to the basic research required to develop and identify new chemical entities, pharmaceutical companies must also engage in research and development to meet FDA requirements. Klett Tr. 247-49; CX 535; CX 541.

FF G 50. Without such research and development, a pharmaceutical company could not commercialize and sell its products in the United States. Thus, in that context, MMD's research and development relating to its finished Cardizem formulations is required and is critical to the exploitation of the products manufactured according to the processes of the '035 patent. Klett Tr. 247-48; Burrows Tr. 2349-50.

FF G 51. Unlike other businesses, there are certain distinctive characteristics of the marketing and promotional activities in the pharmaceutical businesses. In this regard, MMD's product support and marketing activities have significant educational aspects. In addition, there are technical aspects of MMD's marketing and promotional activities. For example, claims made regarding MMD's Cardizem products must be supported by date from various research and development activities, including clinical and comparative studies. Klett Tr. 250-51, 254; Kelly Tr. 172.

FF G 52. In 1991, MMD spent [C] million on research and development. XC 728C.

FF G 53. In 1992, MMD spent approximately [C] million on research and development. CX 728C.

FF G 54. In 1991 and 1992, MMD spent over [C] million in material costs alone for research and development of new formulations of diltiazem. CX 728C.

FF G 55. MMD's Research and Development Department consists of several groups:

[C] CX 496C; CX 649C.

FF G 56. The [C] is further segmented into five functional areas: [C]

[C] These [C] conduct a wide variety of research and development work, including, *inter alia,* toxological, carcinogenic, dose range, and pharmacokinetic studies in animals; drug-drug and food interactions; bioavailability, bioequivalency and stability studies; the manufacture of clinical supplies and dosages for early phase studies; projects devoted to the transition from clinical supply manufacture to large scale manufacture; analytical chemistry support and support to analyze the scientific data collected throughout the drug development process. CX 496C.

FF G 57. The [C] is responsible for the research and development activities relating the FDA-required clinical testing from development phase 1 through phase 3. In phase 1, a drug is first introduced into healthy human volunteers. During phase 2, the drug is introduced to small well-controlled patient populations. In phase 3, the clinical studies are expanded to larger patient populations. At the end of phase 3, the drug is submitted to the FDA for approval. CX 728C; CX 649C.

FF G 58. The [C] is responsible for assuring that the research, development, manufacturing, testing, marketing and distribution of MMD's drugs all comply with governmental regulations. This group interprets and advises MMD on existing and future governmental regulations and verifies and inspects operational programs in light of such regulations and MMD's standard operating procedures. CX 496C.

FF G 59. The [C] is responsible for late phase research of drug products. Late phase research includes those products for which FDA approval is pending (phase 3B) and for those products which have already been approved (phase 4). CX 728C; CX 496C; CX 649C.

FF G 60. MMD has conducted studies to support the filing of its various New Drug Applications (NDA) with the Food and Drug Administration for Cardizem CD and SR capsules, Cardizem tablets, and Cardizem injectable. CX 500C.

FF G 61. The [C] at MMD is responsible for research and development activities relating to FDA-required clinical testing from development phase 1 through phase 3. CX 728C.

FF G 62. MMD submitted its NDA for Cardizem CD capsules for the treatment of hypertension in February 1989, and the NDA was approved in December 1990. CX 728C.

FF G 63. The formulation work on Cardizem CD capsules began in 1985 and continued until MMD submitted its NDA for Cardizem CD capsules for hypertension in February 1989. Fogel Tr. 74-76; CX 728C.

FF G 64. From 1985 to 1989, MMD employed approximately [C] research associates full-time on the development of Cardizem CD capsules; several additional MMD associates devoted a portion of their time to such activities. CX 728C.

FF G 65. MMD spent [C] million to obtain FDA approval for Cardizem CD capsules for the treatment of hypertension. CX 728C.

FF G 66. As part of the research for its NDA for Cardizem CD capsules for hypertension, MMD conducted three large multi-center clinical trials involving over 460 patients. CX 728C.

FF G 67. The clinical trials for the NDA for Cardizem CD capsules for hypertension included a pilot study, a dose response trial, and a dose titration trial. CX 728C; CX 649C; CX 509.

FF G 68. The studies for MMD's NDA on Cardizem CD for hypertension monitored approximately 50 patients over a two-week period. The dose response trial involved approximately 220 patients at 16-20 sites over a six-month period. The dose titration trial involved approximately 120 patients at 8-10 sites throughout the United States. CX 728C.

FF G 69. The clinical trials conducted by MMD to support its NDA for Cardizem CD capsules for hypertension involved approximately [C] MMD associates on a full time basis and [C] on a part-time basis. CX 728C.

FF G 70. The data from the three clinical trials for MMD's NDA on Cardizem CD for hypertension, comprising approximately 100 volumes, were submitted to the NDA in February 1989. This NDA was approved in December 1990. CX 728C.

FF G 71. In January 1992, MMD submitted its NDA for Cardizem CD for the treatment of angina. This NDA was approved in September 1992. CX 728C.

FF G 72. MMD expended [C] million to obtain FDA approval for Cardizem CD capsules in the treatment of angina. CX 728C.

FF G 73. For its NDA on Cardizem CD for angina, MMD conducted two large multi-center clinical trials, a dose response study and a clinical evaluation of Cardizem CD in patients receiving concomitant anti-angina therapy. CX 728C; CX 649C.

FF G 74. The clinical trials for the NDA on Cardizem CD for angina were conducted at 35-40 sites across the United States, involving 350-400 patients at a cost of [C] million. CX 728C.

FF G 75. Approximately [C] MMD associates worked full time on the clinical trials to support the NDA for Cardizem CD for angina and numerous other MMD associates were involved on a part-time basis. CX 728C.

FF G 76. MMD also conducted extensive research and development at significant cost to support is NDA for Cardizem injectables. Additional Cardizem injectable research and development included the development of a lyophilized infusion package and certain drug compatibility studies. CX 495.

FF G 77. There is continuing interaction between MMD and the FDA relating to MMD's Cardizem products. CX 728C; CX 649C.

FF G 78. Recently, MMD initiated a study comparing [C] with Cardizem CD for the treatment of hypertension. CX 728.

FF G 79. The clinical trials for the [C] diltiazem study will cost MMD over [C] per patient and involve [C] patients with hypertension. CX 728C.

FF G 80. MMD is also considering a similar study comparing the use of [C] with Cardizem CD capsules in

the treatment of angina. This study will involve additional expenditures by MMD. CX 728C.

FF G 81. MMD will be making further substantial investments in comparing its Cardizem products to other drugs used in the treatment of various cardiovascular conditions. This study will involve both internal and external costs. Approximately [C] MMD associates will be involved full time in this study. The clinical trials will cost MMD approximately [C] per patient and approximately 100 patients will be included. In addition, approximately 80 patients will be included at a high per patient cost. CX 649C.

FF G 82. MMD is conducting research toward the [C] of Cardizem. MMD has expended over [C] million in material costs alone for this research in both 1991 and 1992. Fogel Tr. 76; CX 728C.

FF G 83. During 1989-90, MMD conducted research on a [C] product containing diltiazem [C]. CX 728.

FF G 84. During 1989-90, MMD also conducted research on a [C] CX 728C.

FF G 85. MMD is currently conducting research on formulating a [C] of Cardizem. CX 728C.

FF G 86. MMD's research and development on Tanabe's diltiazem has led to the development of Cardizem CD and Cardizem SR. Fogel Tr. 75-76.

FF G 87. MMD provides extensive marketing and promotion related to its Cardizem product line through a trained sales force which includes comparative test studies, product support, and educational information. Kelly Tr. 166-167, 173-174, 177; Klett Tr. 250; CX 728.

FF G 88. None of MMD's marketing efforts expressly refer to the '035 patent. Kelly Tr. 199-200; CX 728 at ¶ 41, 49.

FF G 89. The articles protected by the '035 patent are the final dosage forms of Cardizem produced by MMD in the United States. *See* Klett Tr. 239-240.

FF G 90. A nexus exists between the bulk diltiazem produced by Tanabe according to the '035 patent in Japan and MMD's activities related to its Cardizem products in the United States. *See* Klett Tr. 239-241.

FF G 91. A rough approximation of a value added analysis resulted in a calculation of over [C]. Klett Tr. 255-256, 261-262; CPX 12, 13.

FF G 92. From an economic perspective, a domestic industry exists in the United States with respect to the '035 patent. *See* Klett Tr. 236-237.

FF G 93. A domestic industry exists even though claim 1 of the '035 patent does not cover the subsequent step of acetylating N-alkylated TZP to produce diltiazem. *See* Klett. Tr. 262-263.

FF G 94. Tanabe's DMF relating to its current process for manufacturing bulk diltiazem HC1 was filed with the FDA on July 7, 1993. Nakao Tr. 371; CX 726.

FF G 95. Complainants currently practice the process disclosed in Tanabe's 1993 DMF (CX 726) to manufacture diltiazem HC1 which consists of the following: [C] Peterson Tr. 115-117, 124; Nakao 366-367, 373; CX 726, 727; CPX 20.

FF G 96. Tanabe's DMF to manufacture bulk diltiazem describes the N-alkylation process and the acetylation process as [C]. Nakao Tr. 427-430; Kende Tr. 496; CX 726; CPX 20.

FF G 97. Tanabe's N-alkylation step to convert TZP into N-alkylated TZP involves [C] Nakao Tr. 428; CX 726.

FF G 98. Under Tanabe's process, a [C] Nakao Tr. 429.

FF G 99. Tanabe's acetylation step to convert N-alkylated TZP into diltiazem HC1 consists of [C] Nakao Tr. 428; CX 726.

FF G 100. If Tanabe were given only the part of the DMF relating to the N-alkylation step (pp. 41-43), and were not given the part of the DMF corresponding to the acetylation step (pp. 44-45), Tanabe would not know how to carry out the acetylation step. Nakao Tr. 429-450.

FF G 101. Tanabe has not changed its current base solvent combination [C] since 1984. Peterson Tr. 116, 121; Nakao Tr. 369.

FF G 102. In 1993 Tanabe modified its process for manufacturing bulk diltiazem (and thus submitted a new DMF to the FDA) by [C]. Peterson TR. 159; Nakao 379-380.

CONCLUSIONS OF LAW

1. The United States International Trade Commission has jurisdiction over the parties and the subject matter of this investigation. Op. at 5.

2. Claim 1 of the '035 patent is invalid for obviousness. Op. at 119.

3. The '035 patent is unenforceable due to inequitable conduct during the reexamination proceedings at the PTO. Op. at 133-134.

4. Complainants have failed to prove that any of the respondents infringe the '035 patent. Op. at 56-57, 68, 73-74.

5. Respondents have imported, sold for importation or sold within the United States after importation products made by the accused processes. Op. at 134.

6. Complainants have established the existence of a domestic industry. Op. at 146.

7. It has not been established that a violation of section 337 has occurred in the importation, sale for importation or sale within the United States after importation of certain diltiazem hydrochloride. Op. at 334.

INITIAL DETERMINATION AND ORDER

Based on the foregoing opinion, findings of fact, conclusions of law, the evidence, and the record as a whole, and having considered all pleadings and arguments as well as proposed findings of fact and conclusions of law, it is the Administrative Law Judge's INITIAL DETERMINATION ("ID") that no violation of § 337 exists in the importation of certain diltiazem hydrochloride and diltiazem preparations, or in their sale, by reason of infringement of claim 1 of U.S. Letters Patent No. 4,438,035.

The Administrative Law Judge hereby CERTIFIES to the Commission this ID, together with the record of the hearing in this investigation consisting of the following:

1. The transcript of the hearing, with appropriate corrections as may hereafter be ordered by the Administrative Law Judge; and further

2. The exhibits accepted into evidence in this investigation as listed in the attached exhibit lists.

In accordance with Commission Interim Rule 210-44(b), all material found to be confidential by the Administrative Law Judge under Rule 210.6 is to be given *in camera* treatment.

The Secretary shall serve a public version of this ID upon all parties of record and the confidential version upon counsel who are signatories to the protective order issued by the Administrative Law Judge in this investigation, and the Commission Investigative Attorney. To expedite service of the public version, counsel are hereby ordered to serve on the Administrative Law Judge by no later than February 10, 1995, a copy of this ID with those sections considered by the party to be confidential bracketed in red.

This ID shall become the determination of the Commission 45 days after its date of service unless the Commission within those 45 days shall have ordered review of this ID or certain issues herein, pursuant to Commission Interim Rule 210.54(b) or 210.55.

/s/ Sidney Harris
Sidney Harris
Administrative Law Judge

Issued: February 1, 1995

STATUTES

§1337 Unfair practices in import trade.

(a) Unlawful activities; cover industries; definitions

(1) Subject to paragraph (2), the following are unlawful, and when found by the Commission to exist shall be dealt with, in addition to any other provision of law, as provided in this section:

(A) * * * *

(B) The importation into the United States, the sale for importation, or the sale within the United States after importation by the owner, importer, or consignee or articles that –

(i) infringe a valid and enforceable United States patent or a valid and enforceable United States copyright registered under Title 17; or

(ii) are made, produced, processed, or mined under, or by means of, a process covered by the claims of a valid and enforceable United States patent.

(C) * * * *

(D) * * * *

(2) Subparagraphs (B), (C), and (D) of paragraph (1) apply only if an industry in the United States, relating to the articles protected by the patent, copyright, trademark, or mask work concerned, exists or is in the process of being established.

* * *

(c) Determinations; review

The Commission shall determine, with respect to each investigation conducted by it under this section, whether or not there is a violation of this section * * * * Any person adversely affected by a final determination of the Commission under subsection (d), (e), (f), or (g) of this section may appeal such determination within 60 days after the determination becomes final, to the United States Court of Appeals for the Federal Circuit for review in accordance with chapter 7 of Title 5. * * * *

19 U.S.C. §1337(a) & (c) (1997)

WARNER-JENKINSON COMPANY, INC., Petitioner

v.

HILTON DAVIS CHEMICAL CO.

No. 95-728.

Argued Oct. 15, 1996.

Decided March 3, 1997.

Patentee brought infringement action against competitor, alleging that competitor's ultrafiltration method for purifying dye infringed patented method under doctrine of equivalents. The United States District Court for the Southern District of Ohio, Herman J. Weber, J., entered judgment in favor of patentee, and competitor appealed. The Court of Appeals of the Federal Circuit affirmed, 62 F.3d 1512, and certiorari was granted. The Supreme Court, Justice Thomas, held that: (1) doctrine of equivalents is not inconsistent with Patent Act; (2) doctrine of equivalents must be applied to individual elements of patent claim, not to invention as a whole; (3) prosecution history estoppel does not apply whenever patent claim has been amended during application process, regardless of reasons for change; (4) patentee's addition of lower pH limit during application process did necessarily preclude application of doctrine of equivalents as to that element; (5) remand was required to determine whether reason for amending patent claim to add lower pH limit was sufficient to avoid prosecution history estoppel; (6) doctrine of equivalents does not require proof of intent; (7) doctrine of equivalents is not limited to equivalents disclosed within patent itself.

Reversed and remanded.

Justice Ginsburg filed concurring opinion in which Justice Kennedy joined.

Richard G. Taranto, Washington, DC, for petitioner.

Lawrence G. Wallace, Washington, DC, amicus curiae for U.S.

David E. Schmit, Cincinnati, OH, for respondent.

For U.S. Supreme Court briefs see:

1996 WL 172235 (Pet.Brief)
1996 WL 249502 (Resp.Brief)
1996 WL 325332 (Reply.Brief)

Justice THOMAS delivered the opinion of the Court.

Nearly 50 years ago, this Court in *Graver Tank & Mfg. Co. v. Linde Air Products Co.*, 339 U.S. 605, 70 S.Ct. 854, 94 L.Ed. 1097 (1950), set out the modern contours of what is known in patent law as the "doctrine of equivalents." Under this doctrine, a product or process that does not literally infringe upon the express terms of a patent claim may nonetheless be found to infringe if there is "equivalence" between the elements of the accused product or process and the claimed elements of the patented invention. *Id.*, at 609, 70 S.Ct., at 856-857. Petitioner, which was found to have infringed upon respondent's patent under the doctrine of equivalents, invites us to speak the death of that doctrine. We decline that invitation. The significant disagreement within the Court of Appeals for the Federal Circuit concerning the application of *Graver Tank* suggests, however, that the doctrine is not free from confusion. We therefore will endeavor to clarify the proper scope of the doctrine.

I

The essential facts of this case are few. Petitioner Warner-Jenkinson Co. and respondent Hilton Davis Chemical Co. manufacture dyes. Impurities in those dyes must be removed. Hilton Davis holds United States Patent No. 4,560,746 ('746 patent), which discloses an improved purification process involving "ultrafiltration." The '746 process filters impure dye through a porous membrane at certain pressures and pH levels,[1] resulting in a high purity dye product.

The '746 patent issued in 1985. As relevant to this case, the patent claims as its invention an improvement in the ultrafiltration process as follows:

> "In a process for the purification of a dye . . . the improvement which comprises: subjecting an aqueous solution . . . to ultrafiltration through a membrane having a nominal pore diameter of 5-15 Angstroms under a hydrostatic pressure of approximately 200 to 400 p.s.i.g., *at a pH from*

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[1] The pH, or power (exponent) of Hydrogen, of a solution is a measure of its acidity or alkalinity. A pH of 7.0 is neutral; a pH below 7.0 is acidic; and a pH above 7.0 is alkaline. Although measurement of pH is on a logarithmic scale, with each whole number difference representing a ten-fold difference in acidity, the practical significance of any such difference will often depend on the context. Pure water, for example, has a neutral pH of 7.0, whereas carbonated water has an acidic pH of 3.0, and concentrated hydrochloric acid has a pH approaching 0.0. On the other end of the scale, milk of magnesia has a pH of 10.0, whereas household ammonia has a pH of 11.9. 21 Encyclopedia Americana 844 (Int'l ed.1990).

> *approximately 6.0 to 9.0*, to thereby cause separation of said impurities from said dye. . . . " App. 36-37 (emphasis added).

The inventors added the phrase "at a pH from approximately 6.0 to 9.0" during patent prosecution. At a minimum, this phrase was added to distinguish a previous patent (the "Booth" patent) that disclosed an ultrafiltration process operating at a pH above 9.0. The parties disagree as to why the low-end pH limit of 6.0 was included as part of the claim.[2]

In 1986, Warner-Jenkinson developed an ultrafiltration process that operated with membrane pore diameters assumed to be 5-15 Angstroms, at pressures of 200 to nearly 500 p.s.i.g., and at a pH of 5.0. Warner-Jenkinson did not learn of the '746 patent until after it had begun commercial use of its ultrafiltration process. Hilton Davis eventually learned of Warner-Jenkinson's use of ultrafiltration and, in 1991, sued Warner-Jenkinson for patent infringement.

As trial approached, Hilton Davis conceded that there was no literal infringement, and relied solely on the doctrine of equivalents. Over Warner-Jenkinson's objection that the doctrine of equivalents was an equitable

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[2] Petitioner contends that the lower limit was added because below a pH of 6.0 the patented process created "foaming" problems in the plant and because the process was not shown to work below that pH level. Brief for Petitioner 4, n. 5, 37, n. 28. Respondent counters that the process was successfully tested to pH levels as low as 2.2 with no effect on the process because of foaming, but offers no particular explanation as to why the lower level of 6.0 pH was selected. Brief for Respondent 34, n. 34.

doctrine to be applied by the court, the issue of equivalence was included among those sent to the jury. The jury found that the '746 patent was not invalid and that Warner-Jenkinson infringed upon the patent under the doctrine of equivalents. The jury also found, however, that Warner-Jenkinson had not intentionally infringed, and therefore awarded only 20% of the damages sought by Hilton Davis. The District Court denied Warner-Jenkinson's post-trial motions, and entered a permanent injunction prohibiting Warner-Jenkinson from practicing ultrafiltration below 500 p.s.i.g. and below 9.01 pH. A fractured en banc Court of Appeals for the Federal Circuit affirmed. 62 F.3d 1512 (C.A.Fed.1995).

The majority below held that the doctrine of equivalents continues to exist and that its touchstone is whether substantial differences exist between the accused process and the patented process. *Id.*, at 1521-1522. The court also held that the question of equivalence is for the jury to decide and that the jury in this case had substantial evidence from which it could conclude that the Warner-Jenkinson process was not substantially different from the ultrafiltration process disclosed in the '746 patent. *Id.*, at 1525.

There were three separate dissents, commanding a total of 5 of 12 judges. Four of the five dissenting judges viewed the doctrine of equivalents as allowing an improper expansion of claim scope, contrary to this Court's numerous holdings that it is the claim that defines the invention and gives notice to the public of the limits of the patent monopoly. *Id.*, at 1537-1538 (Plager, J., dissenting). The fifth dissenter, the late Judge Nies, was able to reconcile the prohibition against enlarging the

scope of claims and the doctrine of equivalents by applying the doctrine to each element of a claim, rather than to the accused product or process "overall." *Id.*, at 1574 (Nies, J., dissenting). As she explained it, "[t]he 'scope' is not enlarged if courts do not go beyond the substitution of equivalent elements." *Ibid.* All of the dissenters, however, would have found that a much narrowed doctrine of equivalents may be applied in whole or in part by the court. *Id.*, at 1540-1542 (Plager, J., dissenting); *id.*, at 1579 (Nies, J., dissenting).

We granted certiorari, 516 U.S. ___, 116 S.Ct. 1014, 134 L.Ed.2d 95 (1996), and now reverse and remand.

II

In *Graver Tank* we considered the application of the doctrine of equivalents to an accused chemical composition for use in welding that differed from the patented welding material by the substitution of one chemical element. 339 U.S., at 610, 70 S.Ct., at 857. The substituted element did not fall within the literal terms of the patent claim, but the Court nonetheless found that the "question which thus emerges is whether the substitution [of one element for the other] . . . is a change of such substance as to make the doctrine of equivalents inapplicable; or conversely, whether under the circumstances the change was so insubstantial that the trial court's invocation of the doctrine of equivalents was justified." *Ibid.* The Court also described some of the considerations that go into applying the doctrine of equivalents:

> "What constitutes equivalency must be determined against the context of the patent, the

> prior art, and the particular circumstances of the case. Equivalence, in the patent law, is not the prisoner of a formula and is not an absolute to be considered in a vacuum. It does not require complete identity for every purpose and in every respect. In determining equivalents, things equal to the same thing may not be equal to each other and, by the same token, things for most purposes different may sometimes be equivalents. Consideration must be given to the purpose for which an ingredient is used in a patent, the qualities it has when combined with the other ingredients, and the function which it is intended to perform. An important factor is whether persons reasonably skilled in the art would have known of the interchangeability of an ingredient not contained in the patent with one that was." *Id.*, at 609, 70 S.Ct., at 856-857.

Considering those factors, the Court viewed the difference between the chemical element claimed in the patent and the substitute element to be "colorable only," and concluded that the trial court's judgment of infringement under the doctrine of equivalents was proper. *Id.*, at 612, 70 S.Ct., at 858.

A

Petitioner's primary argument in this Court is that the doctrine of equivalents, as set out in *Graver Tank* in 1950, did not survive the 1952 revision of the Patent Act, 35 U.S.C. § 100 *et seq.*, because it is inconsistent with several aspects of that Act. In particular, petitioner argues: (1) the doctrine of equivalents is inconsistent with the statutory requirement that a patentee specifically "claim" the invention covered by a patent, 35 U.S.C.

§ 112; (2) the doctrine circumvents the patent reissue process – designed to correct mistakes in drafting or the like – and avoids the express limitations on that process, 35 U.S.C. §§ 251-252; (3) the doctrine is inconsistent with the primacy of the Patent and Trademark Office (PTO) in setting the scope of a patent through the patent prosecution process; and (4) the doctrine was implicitly rejected as a general matter by Congress' specific and limited inclusion of the doctrine in one section regarding "means" claiming, 35 U.S.C. § 112, ¶ 6. All but one of these arguments were made in *Graver Tank* in the context of the 1870 Patent Act, and failed to command a majority.[3]

The 1952 Patent Act is not materially different from the 1870 Act with regard to claiming, reissue, and the role

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[3] *Graver Tank* was decided over a vigorous dissent. In that dissent, Justice Black raised the first three of petitioner's four arguments against the doctrine of equivalents. See 339 U.S., at 613-614, 70 S.Ct., at 858-859 (doctrine inconsistent with statutory requirement to "distinctly claim" the invention); *id.*, at 614-615, 70 S.Ct., at 859-860 (patent reissue process available to correct mistakes); *id.*, at 615, n. 3, 70 S.Ct., at 859, n. 3 (duty lies with the Patent Office to examine claims and to conform them to the scope of the invention; inventors may appeal Patent Office determinations if they disagree with result).

Indeed, petitioner's first argument was not new even in 1950. Nearly 100 years before *Graver Tank*, this Court approved of the doctrine of equivalents in *Winans v. Denmead*, 15 How. 330, 14 L.Ed. 717 (1854). The dissent in *Winans* unsuccessfully argued that the majority result was inconsistent with the requirement in the 1836 Patent Act that the applicant "particularly 'specify and point' out what he claims as his invention," and that the patent protected nothing more. *Id.*, 15 How. at 347 (Campbell, J., dissenting).

of the PTO. Compare, *e.g.*, 35 U.S.C. § 112 ("The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention") with The Consolidated Patent Act of 1870, ch. 230, § 26, 16 Stat. 198, 201 (the applicant "shall particularly point out and distinctly claim the part, improvement, or combination which he claims as his invention or discovery"). Such minor differences as exist between those provisions in the 1870 and the 1952 Acts have no bearing on the result reached in *Graver Tank*, and thus provide no basis for our overruling it. In the context of infringement, we have already held that pre-1952 precedent survived the passage of the 1952 Act. See *Aro Mfg. Co. v. Convertible Top Replacement Co.*, 365 U.S. 336, 342, 81 S.Ct. 599, 602-603, 5 L.Ed.2d 592 (1961) (new section defining infringement "left intact the entire body of case law on direct infringement"). We see no reason to reach a different result here.[4]

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[4] Petitioner argues that the evolution in patent practice from "central" claiming (describing the core principles of the invention) to "peripheral" claiming (describing the outer boundaries of the invention) requires that we treat *Graver Tank* as an aberration and abandon the doctrine of equivalents. Brief for Petitioner 43-45. We disagree. The suggested change in claiming practice predates *Graver Tank*, is not of statutory origin, and seems merely to reflect narrower inventions in more crowded arts. Also, judicial recognition of so-called "pioneer" patents suggests that the abandonment of "central" claiming may be overstated. That a claim describing a limited improvement in a crowded field will have a limited range of permissible equivalents does not negate the availability of the doctrine *vel non*.

Petitioner's fourth argument for an implied congressional negation of the doctrine of equivalents turns on the reference to "equivalents" in the "means" claiming provision of the 1952 Act. Section 112, ¶ 6, a provision not contained in the 1870 Act, states:

> "An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification *and equivalents thereof.*" (Emphasis added.)

Thus, under this new provision, an applicant can describe an element of his invention by the result accomplished or the function served, rather than describing the item or element to be used (*e.g.*, "a means of connecting Part A to Part B," rather than "a two-penny nail"). Congress enacted § 112, ¶ 6 in response to *Halliburton Oil Well Cementing Co. v. Walker*, which rejected claims that "do not describe the invention but use 'conveniently functional language at the exact point of novelty,' " 329 U.S. 1, 8, 67 S.Ct. 6, 9-10, 91 L.Ed. 3 (1946) (citation omitted). See *In re Donaldson Co.*, 16 F.3d 1189, 1194 (C.A.Fed.1994) (Congress enacted predecessor of § 112, ¶ 6 in response to *Halliburton*); *In re Fuetterer*, 50 C.C.P.A. 1453, 319 F.2d 259, 264, n. 11 (1963) (same); see also, 2 D. Chisum, Patents § 8.04[2], at 63-64 (1996) (discussing 1954 commentary of then-Chief Patent Examiner P.J. Federico). Section 112, ¶ 6 now expressly allows so-called "means" claims, with the proviso that application of the broad literal language of such claims must be limited to only those means that are "equivalent" to the actual means shown in the patent

specification. This is an application of the doctrine of equivalents in a restrictive role, narrowing the application of broad literal claim elements. We recognized this type of role for the doctrine of equivalents in *Graver Tank* itself. 339 U.S., at 608-609, 70 S.Ct., at 856-857. The added provision, however, is silent on the doctrine of equivalents as applied where there is no literal infringement.

Because § 112, ¶ 6 was enacted as a targeted cure to a specific problem, and because the reference in that provision to "equivalents" appears to be no more than a prophylactic against potential side effects of that cure, such limited congressional action should not be overread for negative implications. Congress in 1952 could easily have responded to *Graver Tank* as it did to the *Halliburton* decision. But it did not. Absent something more compelling than the dubious negative inference offered by petitioner, the lengthy history of the doctrine of equivalents strongly supports adherence to our refusal in *Graver Tank* to find that the Patent Act conflicts with that doctrine. Congress can legislate the doctrine of equivalents out of existence any time it chooses. The various policy arguments now made by both sides are thus best addressed to Congress, not this Court.

B

We do, however, share the concern of the dissenters below that the doctrine of equivalents, as it has come to be applied since *Graver Tank*, has taken on a life of its own, unbounded by the patent claims. There can be no denying that the doctrine of equivalents, when applied broadly, conflicts with the definitional and public-notice

functions of the statutory claiming requirement. Judge Nies identified one means of avoiding this conflict:

> "[A] distinction can be drawn that is not too esoteric between substitution of an equivalent for a component *in* an invention and enlarging the metes and bounds of the invention *beyond* what is claimed.
>
> . . . .
>
> "Where a claim to an invention is expressed as a combination of elements, as here, 'equivalents' in the sobriquet 'Doctrine of Equivalents' refers to the equivalency of an *element* or *part* of the invention with one that is substituted in the accused product or process.
>
> . . . .
>
> "This view that the accused device or process must be more than 'equivalent' *overall* reconciles the Supreme Court's position on infringement by equivalents with its concurrent statements that 'the courts have no right to enlarge a patent beyond the scope of its claims as allowed by the Patent Office.' [Citations omitted.] The 'scope' is not enlarged if courts do not go beyond the substitution of equivalent elements." 62 F.3d, at 1573-1574 (Nies, J., dissenting) (emphasis in original).

We concur with this apt reconciliation of our two lines of precedent. Each element contained in a patent claim is deemed material to defining the scope of the patented invention, and thus the doctrine of equivalents must be applied to individual elements of the claim, not to the invention as a whole. It is important to ensure that the application of the doctrine, even as to an individual

element, is not allowed such broad play as to effectively eliminate that element in its entirety. So long as the doctrine of equivalents does not encroach beyond the limits just described, or beyond related limits to be discussed *infra*, at 1047-1048, 1053, n. 8, and 1054-1055, we are confident that the doctrine will not vitiate the central functions of the patent claims themselves.

III

Understandably reluctant to assume this Court would overrule *Graver Tank*, petitioner has offered alternative arguments in favor of a more restricted doctrine of equivalents than it feels was applied in this case. We address each in turn.

A

Petitioner first argues that *Graver Tank* never purported to supersede a well-established limit on non-literal infringement, known variously as "prosecution history estoppel" and "file wrapper estoppel." See *Bayer Aktiengesellschaft v. Duphar Int'l Research B.V.*, 738 F.2d 1237, 1238 (C.A.Fed.1984). According to petitioner, any surrender of subject matter during patent prosecution, regardless of the reason for such surrender, precludes recapturing any part of that subject matter, even if it is equivalent to the matter expressly claimed. Because, during patent prosecution, respondent limited the pH element of its claim to pH levels between 6.0 and 9.0, petitioner would have those limits form bright lines beyond which no equivalents may be claimed. Any inquiry into the reasons for a surrender, petitioner claims,

would undermine the public's right to clear notice of the scope of the patent as embodied in the patent file.

We can readily agree with petitioner that *Graver Tank* did not dispose of prosecution history estoppel as a legal limitation on the doctrine of equivalents. But petitioner reaches too far in arguing that the reason for an amendment during patent prosecution is irrelevant to any subsequent estoppel. In each of our cases cited by petitioner and by the dissent below, prosecution history estoppel was tied to amendments made to avoid the prior art, or otherwise to address a specific concern – such as obviousness – that arguably would have rendered the claimed subject matter unpatentable. Thus, in *Exhibit Supply Co. v. Ace Patents Corp.*, Chief Justice Stone distinguished inclusion of a limiting phrase in an original patent claim from the "very different" situation in which "the applicant, in order to meet objections in the Patent Office, *based on references to the prior art*, adopted the phrase as a substitute for the broader one" previously used. 315 U.S. 126, 136, 62 S.Ct. 513, 518, 86 L.Ed. 736 (1942) (emphasis added). Similarly, in *Keystone Driller Co. v. Northwest Engineering Corp.*, 294 U.S. 42, 55 S.Ct. 262, 79 L.Ed. 747 (1935), estoppel was applied where the initial claims were "rejected on the prior art," *id.*, at 48, n. 6, 55 S.Ct., at 265, n. 6, and where the allegedly infringing equivalent element was outside of the revised claims and within the prior art that formed the basis for the rejection of the earlier claims, *id.*, at 48, 55 S.Ct., at 264-265.[5]

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[5] See also, *Smith v. Magic City Kennel Club, Inc.*, 282 U.S. 784, 788, 51 S.Ct. 291, 293, 75 L.Ed. 707 (1931) (estoppel applied to amended claim where the original "claim was rejected on the

It is telling that in each case this Court probed the reasoning behind the Patent Office's insistence upon a change in the claims. In each instance, a change was demanded because the claim as otherwise written was viewed as not describing a patentable invention at all – typically because what it described was encompassed within the prior art. But, as the United States informs us, there are a variety of other reasons why the PTO may request a change in claim language. Brief for United States as *Amicus Curiae* 22-23 (counsel for the PTO also appearing on the brief). And if the PTO has been requesting changes in claim language without the intent to limit equivalents or, indeed, with the expectation that language it required would in many cases allow for a range of equivalents, we should be extremely reluctant to upset the basic assumptions of the PTO without substantial reason for doing so. Our prior cases have consistently

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prior patent to" another); *Computing Scale Co. of America v. Automatic Scale Co.*, 204 U.S. 609, 618-620, 27 S.Ct. 307, 311-312, 51 L.Ed. 645 (1907) (initial claims rejected based on lack of invention over prior patents); *Hubbell v. United States*, 179 U.S. 77, 83, 21 S.Ct. 24, 26-27, 45 L.Ed. 95 (1900) (patentee estopped from excluding a claim element where element was added to overcome objections based on lack of novelty over prior patents); *Sutter v. Robinson*, 119 U.S. 530, 541, 7 S.Ct. 376, 381-382, 30 L.Ed. 492 (1886) (estoppel applied where, during patent prosecution, the applicant "was expressly required to state that [the device's] structural plan was old and not of his invention"); cf. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 33, 86 S.Ct. 684, 701-702, 15 L.Ed.2d 545 (1966) (noting, in a validity determination, that "claims that have been narrowed in order to obtain the issuance of a patent by distinguishing the prior art cannot be sustained to cover that which was previously by limitation eliminated from the patent").

applied prosecution history estoppel only where claims have been amended for a limited set of reasons, and we see no substantial cause for requiring a more rigid rule invoking an estoppel regardless of the reasons for a change.[6]

In this case, the patent examiner objected to the patent claim due to a perceived overlap with the Booth patent, which revealed an ultrafiltration process operating at a pH above 9.0. In response to this objection, the phrase "at a pH from approximately 6.0 to 9.0" was added to the claim. While it is undisputed that the upper limit of 9.0 was added in order to distinguish the Booth patent, the reason for adding the lower limit of 6.0 is unclear. The lower limit certainly did not serve to distinguish the Booth patent, which said nothing about pH levels below 6.0. Thus, while a lower limit of 6.0, by its mere inclusion, became a material *element* of the claim, that did not necessarily preclude the application of the doctrine of equivalents as to that element. See *Hubbell v. United States*, 179 U.S. 77, 82, 21 S.Ct. 24, 26, 45 L.Ed. 95 (1900) (" '[A]ll [specified elements] must be regarded as material,' " though it remains an open " 'question

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[6] That petitioner's rule might provide a brighter line for determining whether a patentee is estopped under certain circumstances is not a sufficient reason for adopting such a rule. This is especially true where, as here, the PTO may have relied upon a flexible rule of estoppel when deciding whether to ask for a change in the first place. To change so substantially the rules of the game now could very well subvert the various balances the PTO sought to strike when issuing the numerous patents which have not yet expired and which would be affected by our decision.

whether an omitted part is supplied by an equivalent device or instrumentality' " (citation omitted)). Where the reason for the change was not related to avoiding the prior art, the change may introduce a new element, but it does not necessarily preclude infringement by equivalents of that element.[7]

We are left with the problem, however, of what to do in a case like the one at bar, where the record seems not to reveal the reason for including the lower pH limit of 6.0. In our view, holding that certain reasons for a claim amendment may avoid the application of prosecution history estoppel is not tantamount to holding that the *absence* of a reason for an amendment may similarly avoid such an estoppel. Mindful that claims do indeed serve both a definitional and a notice function, we think the better rule is to place the burden on the patent-holder to establish the reason for an amendment required during patent prosecution. The court then would decide whether that reason is sufficient to overcome prosecution history estoppel as a bar to application of the doctrine of equivalents to the element added by that amendment. Where no

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[7] We do not suggest that, where a change is made to overcome an objection based on the prior art, a court is free to review the correctness of that objection when deciding whether to apply prosecution history estoppel. As petitioner rightly notes, such concerns are properly addressed on direct appeal from the denial of a patent, and will not be revisited in an infringement action. *Smith v. Magic City Kennel Club, Inc., supra,* 282 U.S. at 789-790, 51 S.Ct., at 293-294. What *is* permissible for a court to explore is the reason (right or wrong) for the objection and the manner in which the amendment addressed and avoided the objection.

explanation is established, however, the court should presume that the PTO had a substantial reason related to patentability for including the limiting element added by amendment. In those circumstances, prosecution history estoppel would bar the application of the doctrine equivalents as to that element. The presumption we have described, one subject to rebuttal if an appropriate reason for a required amendment is established, gives proper deference to the role of claims in defining an invention and providing public notice, and to the primacy of the PTO in ensuring that the claims allowed cover only subject matter that is properly patentable in a proffered patent application. Applied in this fashion, prosecution history estoppel places reasonable limits on the doctrine of equivalents, and further insulates the doctrine from any feared conflict with the Patent Act.

Because respondent has not proffered in this Court a reason for the addition of a lower pH limit, it is impossible to tell whether the reason for that addition could properly avoid an estoppel. Whether a reason in fact exists, but simply was not adequately developed, we cannot say. On remand, the Federal Circuit can consider whether reasons for that portion of the amendment were offered or not and whether further opportunity to establish such reasons would be proper.

B

Petitioner next argues that even if *Graver Tank* remains good law, the case held only that the absence of substantial differences was a *necessary* element for infringement under the doctrine of equivalents, not that it

was *sufficient* for such a result. Brief for Petitioner 32. Relying on *Graver Tank*'s references to the problem of an "unscrupulous copyist" and "piracy," 339 U.S., at 607, 70 S.Ct., at 855-856, petitioner would require judicial exploration of the equities of a case before allowing application of the doctrine of equivalents. To be sure, *Graver Tank* refers to the prevention of copying and piracy when describing the benefits of the doctrine of equivalents. That the doctrine produces such benefits, however, does not mean that its application is limited only to cases where those particular benefits are obtained.

Elsewhere in *Graver Tank* the doctrine is described in more neutral terms. And the history of the doctrine as relied upon by *Graver Tank* reflects a basis for the doctrine not so limited as petitioner would have it. In *Winans v. Denmead*, 15 How. 330, 343, 14 L.Ed. 717 (1854), we described the doctrine of equivalents as growing out of a legally implied term in each patent claim that "the claim extends to the thing patented, however its form or proportions may be varied." Under that view, application of the doctrine of equivalents involves determining whether a particular accused product or process infringes upon the patent claim, where the claim takes the form – half express, half implied – of "X and its equivalents."

Union Paper-Bag Machine Co. v. Murphy, 97 U.S. 120, 125, 24 L.Ed. 935 (1878), on which *Graver Tank* also relied, offers a similarly intent-neutral view of the doctrine of equivalents:

> "[T]he substantial equivalent of a thing, in the sense of the patent law, is the same as the thing itself; so that if two devices do the same work in

> substantially the same way, and accomplish substantially the same result, they are the same, even though they differ in name, form, or shape."

If the essential predicate of the doctrine of equivalents is the notion of identity between a patented invention and its equivalent, there is no basis for treating an infringing equivalent any differently than a device that infringes the express terms of the patent. Application of the doctrine of equivalents, therefore, is akin to determining literal infringement, and neither requires proof of intent.

Petitioner also points to *Graver Tank*'s seeming reliance on the absence of independent experimentation by the alleged infringer as supporting an equitable defense to the doctrine of equivalents. The Federal Circuit explained this factor by suggesting that an alleged infringer's behavior, be it copying, designing around a patent, or independent experimentation, indirectly reflects the substantiality of the differences between the patented invention and the accused device or process. According to the Federal Circuit, a person aiming to copy or aiming to avoid a patent is imagined to be at least marginally skilled at copying or avoidance, and thus intentional copying raises an inference – rebuttable by proof of independent development – of having only insubstantial differences, and intentionally designing around a patent claim raises an inference of substantial differences. This explanation leaves much to be desired. At a minimum, one wonders how ever to distinguish between the intentional copyist making minor changes to

lower the risk of legal action, and the incremental innovator designing around the claims, yet seeking to capture as much as is permissible of the patented advance.

But another explanation is available that does not require a divergence from generally objective principles of patent infringement. In both instances in *Graver Tank* where we referred to independent research or experiments, we were discussing the known interchangeability between the chemical compound claimed in the patent and the compound substituted by the alleged infringer. The need for independent experimentation thus could reflect knowledge – or lack thereof – of interchangeability possessed by one presumably skilled in the art. The known interchangeability of substitutes for an element of a patent is one of the express objective factors noted by *Graver Tank* as bearing upon whether the accused device is substantially the same as the patented invention. Independent experimentation by the alleged infringer would not always reflect upon the objective question whether a person skilled in the art would have known of the interchangeability between two elements, but in many cases it would likely be probative of such knowledge.

Although *Graver Tank* certainly leaves room for petitioner's suggested inclusion of intent-based elements in the doctrine of equivalents, we do not read it as requiring them. The better view, and the one consistent with *Graver Tank*'s predecessors and the objective approach to infringement, is that intent plays no role in the application of the doctrine of equivalents.

C

Finally, petitioner proposes that in order to minimize conflict with the notice function of patent claims, the doctrine of equivalents should be limited to equivalents that are disclosed within the patent itself. A milder version of this argument, which found favor with the dissenters below, is that the doctrine should be limited to equivalents that were known at the time the patent was issued, and should not extend to after-arising equivalents.

As we have noted, *supra*, at 1052, with regard to the objective nature of the doctrine, a skilled practitioner's knowledge of the interchangeability between claimed and accused elements is not relevant for its own sake, but rather for what it tells the factfinder about the similarities or differences between those elements. Much as the perspective of the hypothetical "reasonable person" gives content to concepts such as "negligent" behavior, the perspective of a skilled practitioner provides content to, and limits on, the concept of "equivalence." Insofar as the question under the doctrine of equivalents is whether an accused element is equivalent to a claimed element, the proper time for evaluating equivalency – and thus knowledge of interchangeability between elements – is at the time of infringement, not at the time the patent was issued. And rejecting the milder version of petitioner's argument necessarily rejects the more severe proposition that equivalents must not only be known, but must also be actually disclosed in the patent in order for such equivalents to infringe upon the patent.

IV

The various opinions below, respondents, and *amici* devote considerable attention to whether application of the doctrine of equivalents is a task for the judge or for the jury. However, despite petitioner's argument below that the doctrine should be applied by the judge, in this Court petitioner makes only passing reference to this issue. See Brief for Petitioner 22, n. 15 ("If this Court were to hold in *Markman v. Westview Instruments, Inc.*, No. 95-26, 1996 WL 12585 (argued Jan. 8, 1996), that judges rather than juries are to construe patent claims, so as to provide a uniform definition of the scope of the legally protected monopoly, it would seem at cross-purposes to say that juries may nonetheless expand the claims by resort to a broad notion of 'equivalents' "); Reply Brief for Petitioner 20 (whether judge or jury should apply the doctrine of equivalents depends on how the Court views the nature of the inquiry under the doctrine of equivalents).

Petitioner's comments go more to the alleged inconsistency between the doctrine of equivalents and the claiming requirement than to the role of the jury in applying the doctrine as properly understood. Because resolution of whether, or how much of, the application of the doctrine of equivalents can be resolved by the court is not necessary for us to answer the question presented, we decline to take it up. The Federal Circuit held that it was for the jury to decide whether the accused process was equivalent to the claimed process. There was ample support in our prior cases for that holding. See, *e.g.*, *Union Paper-Bag Machine Co. v. Murphy*, 97 U.S., at 125 ("in determining the question of infringement, the court or

jury, as the case may be, . . . are to look at the machines or their several devices or elements in the light of what they do, or what office or function they perform, and how they perform it, and to find that one thing is substantially the same as another, if it performs substantially the same function in substantially the same way to obtain the same result"); *Winans v. Denmead*, 15 How., at 344 ("[It] is a question for the jury" whether the accused device was "the same in kind, and effected by the employment of [the patentee's] mode of operation in substance"). Nothing in our recent *Markman* decision necessitates a different result than that reached by the Federal Circuit. Indeed, *Markman*, cites with considerable favor, when discussing the role of judge and jury, the seminal *Winans* decision. *Markman v. Westview Instruments, Inc.*, 517 U.S. ___, ___-___, 116 S.Ct. 1384, 1392-1393, 134 L.Ed.2d 577 (1996). Whether, if the issue were squarely presented to us, we would reach a different conclusion than did the Federal Circuit is not a question we need decide today.[8]

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[8] With regard to the concern over unreviewability due to black-box jury verdicts, we offer only guidance, not a specific mandate. Where the evidence is such that no reasonable jury could determine two elements to be equivalent, district courts are obliged to grant partial or complete summary judgment. See Fed. Rule Civ. Proc. 56; *Celotex Corp. v. Catrett*, 477 U.S. 317, 322-323, 106 S.Ct. 2548, 2552-2553, 91 L.Ed.2d 265 (1986). If there has been a reluctance to do so by some courts due to unfamiliarity with the subject matter, we are confident that the Federal Circuit can remedy the problem. Of course, the various legal limitations on the application of the doctrine of equivalents are to be determined by the court, either on a pretrial motion for partial summary judgment or on a motion for judgment as a matter of law at the close of the evidence and after the jury verdict. Fed. Rule Civ. Proc. 56; Fed. Rule Civ.

V

All that remains is to address the debate regarding the linguistic framework under which "equivalence" is determined. Both the parties and the Federal Circuit spend considerable time arguing whether the so-called "triple identity" test – focusing on the *function* served by a particular claim element, the *way* that element serves that function, and the *result* thus obtained by that element – is a suitable method for determining equivalence, or whether an "insubstantial differences" approach is better. There seems to be substantial agreement that, while the triple identity test may be suitable for analyzing mechanical devices, it often provides a poor framework for analyzing other products or processes. On the other hand, the insubstantial differences test offers little additional guidance as to what might render any given difference "insubstantial."

In our view, the particular linguistic framework used is less important than whether the test is probative of the essential inquiry: Does the accused product or process

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Proc. 50. Thus, under the particular facts of a case, if prosecution history estoppel would apply or if a theory of equivalence would entirely vitiate a particular claim element, partial or complete judgment should be rendered by the court, as there would be no further *material* issue for the jury to resolve. Finally, in cases that reach the jury, a special verdict and/or interrogatories on each claim element could be very useful in facilitating review, uniformity, and possibly postverdict judgments as a matter of law. See Fed. Rule Civ. Proc. 49; Fed. Rule Civ. Proc. 50. We leave it to the Federal Circuit how best to implement procedural improvements to promote certainty, consistency, and reviewability to this area of the law.

contain elements identical or equivalent to each claimed element of the patented invention? Different linguistic frameworks may be more suitable to different cases, depending on their particular facts. A focus on individual elements and à special vigilance against allowing the concept of equivalence to eliminate completely any such elements should reduce considerably the imprecision of whatever language is used. An analysis of the role played by each element in the context of the specific patent claim will thus inform the inquiry as to whether a substitute element matches the function, way, and result of the claimed element, or whether the substitute element plays a role substantially different from the claimed element. With these limiting principles as a backdrop, we see no purpose in going further and micro-managing the Federal Circuit's particular word-choice for analyzing equivalence. We expect that the Federal Circuit will refine the formulation of the test for equivalence in the orderly course of case-by-case determinations, and we leave such refinement to that court's sound judgment in this area of its special expertise.

VI

Today we adhere to the doctrine of equivalents. The determination of equivalence should be applied as an objective inquiry on an element-by-element basis. Prosecution history estoppel continues to be available as a defense to infringement, but if the patent-holder demonstrates that an amendment required during prosecution had a purpose unrelated to patentability, a court must consider that purpose in order to decide whether an estoppel is precluded. Where the patentholder is unable

to establish such a purpose, a court should presume that the purpose behind the required amendment is such that prosecution history estoppel would apply. Because the Court of Appeals for the Federal Circuit did not consider all of the requirements as described by us today, particularly as related to prosecution history estoppel and the preservation of some meaning for each element in a claim, we reverse and remand for further proceedings consistent with this opinion.

It is so ordered.

Justice GINSBURG, with whom Justice KENNEDY joins, concurring.

I join the opinion of the Court and write separately to add a cautionary note on the rebuttable presumption the Court announces regarding prosecution history estoppel. I address in particular the application of the presumption in this case and others in which patent prosecution has already been completed. The new presumption, if applied woodenly, might in some instances unfairly discount the expectations of a patentee who had no notice at the time of patent prosecution that such a presumption would apply. Such a patentee would have had little incentive to insist that the reasons for all modifications be memorialized in the file wrapper as they were made. Years after the fact, the patentee may find it difficult to establish an evidentiary basis that would overcome the new presumption. The Court's opinion is sensitive to this problem, noting that "the PTO may have relied upon a flexible rule of estoppel when deciding whether to ask for a change" during patent prosecution. *Ante,* at 1050, n. 6.

Because respondent has not presented to this Court any explanation for the addition of the lower pH limit, I concur in the decision to remand the matter to the Federal Circuit. On remand, that court can determine – bearing in mind the prior absence of clear rules of the game – whether suitable reasons for including the lower pH limit were earlier offered or, if not, whether they can now be established.